



Original Article

Histological heterogeneity of tumours of female genital tract- an observation from commentary box of a tertiary care hospital in eastern India

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Abstract

Cases of gynaecological malignancies are common albeit speculative in some instances owing to the marked sequential cyclic changes the female genital tract undergoes in a lifetime and also the amplitude of heterogeneity it can present with. Five selected cases posing considerable diagnostic challenges are presented here, among the Cases of Gynecological malignancies those were studied over the period of 3 years. Epithelioid leiomyosarcoma involving uterine corpus and unilateral ovary, high grade serous carcinoma with diffuse involvement of bilateral ovaries as well as endometrium and metastasis from occult gall bladder carcinoma to bilateral cystic ovaries are the first three cases. A case of uterine carcinosarcoma in a younger lady and an immature teratoma of ovary presenting with extensive gliomatosis peritonei are included in the last two cases. Each of these cases posed some unique diagnostic challenges as a virtue of their own.

Keywords: *Epithelioid leiomyosarcoma, high grade serous carcinomas, metastatic gall bladder cancer, carcinosarcoma uterus, Immature Teratoma, gliomatosis peritonei.*

Introduction

A majority of the regular turnover of histopathological specimens in a pathology department comprises specimens from female genital tract. A few of them pose considerable challenge in diagnosis even to the senior pathologists or lead to such findings that was not even in the furthest assumption of the clinician. A handful of such astounding cases encountered in a tertiary care hospital of east India is presented here.

A) Ovarian involvement is identified in a case of Leiomyosarcoma uterus, a highly aggressive malignant neoplasm arising from myometrial smooth muscle. The

epithelioid clear cell like morphology of tumour cells, an uncommon phenomenon, posed a significant diagnostic challenge regarding the true nature of the tumour.

B) High grade serous carcinoma was found to involve bilateral ovaries as well as endometrium in a post menopausal lady. The inherent intricacies of diagnosis in this situation and different possibilities are explored here.

C) Adenocarcinomatous involvement was found in bilateral ovaries and also in the removed gall bladder in the same sitting without prior suspicion of any sinister malignant pathology in it. Both the ovaries

containing large cysts complicated the matter further regarding the true identification of the primary.

- D) A case of uterine carcinosarcoma in a 32-year-old woman suffering from menorrhagia for 6 months is presented here. The histological examination revealed that the tumor comprised components of poorly differentiated carcinoma and spindle cell sarcoma presumably fibrosarcoma accompanied by immature chondromatous element.
- E) Fifth one is a case of immature teratoma in a 12 years old girl with high preoperative tumor markers like AFP, CA 125 and CEA levels. Histopathology revealed an immature teratoma grade 3 associated with massive gliomatosis peritonei of omentum and pouch of Douglas.

Case Details

- A) A 49 years old P₁₊₀ post menopausal lady sought gynecologist's advice in the outdoor patients' department of a tertiary care hospital in eastern india for recent onset bleeding per vaginum. The episode started 3 months back with painless copious amount of bleeding associated with an expanding lower abdominal lump. Detailed interrogation revealed evidence of significant weight loss in this narrow time interval.

Imaging studies revealed a huge pelvic mass wrapped by omentum and obscuring the normal pelvic structures possibly originating from uterus. An elective exploratory laparotomy was undertaken soon, debulking was done and specimen was sent for histopathological examination.

Gross Findings: The total surgical specimen was sent in four separate tissue pieces. A large fibroid like growth was found in the posterior uterine corpus seemed to be protruding outside and grossly distorting the endometrial cavity. The specimen labelled as pelvic mass was probably the

right ovary closely related to posterior surface of uterus. On cut section, both the masses were soft, fleshy, whitish with some necrotic areas in between.

Microscopical Examination: Multiple sections were examined from the uterine mass, which showed sheets of round to polygonal cells having centrally placed pleomorphic nuclei with clear cytoplasm admixed with areas of spindle cells. Frequent atypical mitotic figures were seen. Surrounding stroma was hyalinised. Overall impression was that of Epithelioid type leiomyosarcoma. Right ovary was found to be involved, the other ovary and fallopian tube and the excised omentum were free from any tumour process.

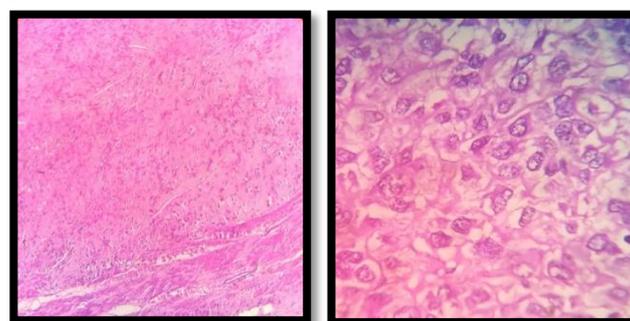


Figure 1: Epithelioid Leiomyosarcoma of clear cell morphology: A. 10X B. 40X

- B) A 55 years old P₂₊₁ lady presented with complaints of post menopausal bleeding per vaginum for last 3 months along with history of significant loss of weight. Clinical as well as radiological examination revealed presence of an abdominopelvic lump with complex bilateral ovarian SOL containing solid components. Additional ultrasound finding showed Focal Irregular thickening of the endometrium in an atrophic background.

An exploratory laparotomy was undertaken soon with completion of total abdominal hysterectomy with bilateral salpingo oophorectomy.

Gross Findings: On gross examination, right and left ovary were found to be replaced by solid cystic structures measuring 5×5×3 cm and 10×5×3cm respectively. Uterus was grossly atrophic

but on cut section showed presence of a friable growth which seemed to have invaded greater than half of the myometrium.

Microscopy: Sections from the endomyometrium as well as from bilateral ovaries showed histopathological features of high grade serous carcinoma. The tumour process involved greater than half of the myometrium without any serosal involvement. Ovarian capsules were intact and intervening fallopian tubes were free from any tumour process.

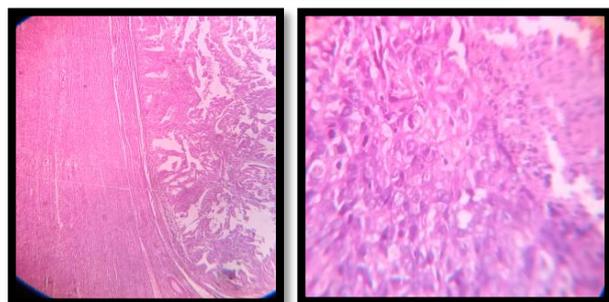


Figure 2: a. gross picture of specimen b. Serous carcinoma invading myometrium c. Ovarian serous carcinoma

C) A 38 years old lady presented with an abdomino-pelvic lump and irregular menstruation for last 6 months. Ultrasound findings revealed presence of bilateral ovarian large multiloculated cystic structures. Non contrast CT confirmed the findings and suggested those can be mucinous cystadenomas of ovarian origin.No significant ascites was there.

As an additional finding, gall bladder showed presence of two large calculi, wall thickness being 6-7 mm. Neither any obvious mass lesion nor any pericholic fluid collection was noted and overall radiological features were suggestive of chronic calculus cholecystitis.

During the time of surgical exploration of abdomen in the operation theatre in department of gynaecology; surgeon was called for removal of gall bladder in the same sitting as decided earlier and both the specimens of TAHBSO and simple cholecystectomy were sent for histopathological examination.

Gross findings: on gross examination, right and left ovary were found to be replaced by two multiloculated cystic structures measuring 17× 16× 7cm and 14× 8 ×3cm respectively. serous fluid was drained out on cut section. No solid area noted inside the cyst, neither there was any surface breach.

The gall bladder was also apparently normal without any mass lesion except the wall thickness was 8 mm.

Microscopy: Sections from the gall bladder revealed histopathological features of moderately differentiated adenocarcinoma involving upto serosa with dysplasia in the lining epithelium at places.

Both the ovaries showed presence of metastatic deposit of adenocarcinoma in the background of multiloculated serous cyst; creating gruesome concern regarding consideration of an ovarian primary.

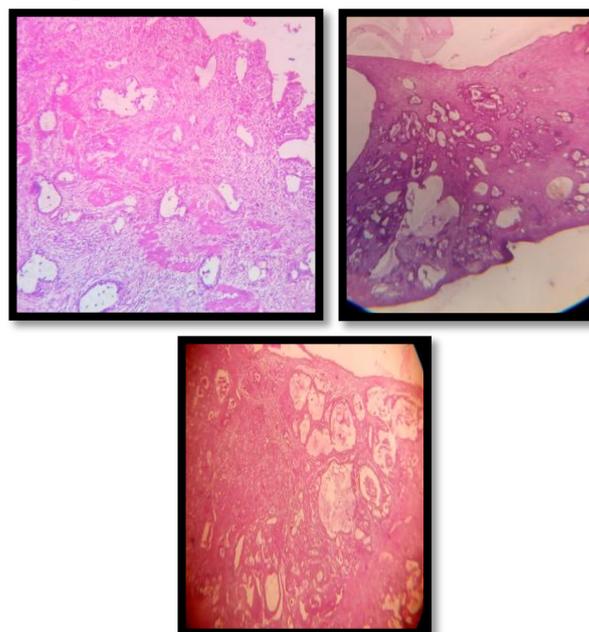


Figure 3: a. Adenocarcinoma Gall bladder b. metastasis in cystic Right ovary c. Metastasis in cystic Left ovary

D) A 32 year old woman admitted to hospital with complaints of menometrorrhagia and abdominal pain of 6 months duration. Endometrial biopsy was suspicious of carcinoma of uterus. Total abdominal hysterectomy with bilateralsalpingo-oophorectomy was done.

Gross: On gross examination of the specimen: The anatomy was grossly distorted, uterus and part of cervix measured (16X9X7) cm. Some necrotic, haemorrhagic tissue were obtained from uterine cavity.

Microscopy: On histopathological examination, tissue from uterocervical junction and necrosed area from uterine cavity and right sided broad ligament show areas poorly differentiated carcinoma and spindle cell sarcoma presumably fibrosarcoma with immature chondromatous element. Epithelial components showed poorly differentiated areas with some glandular structures lined by cells having pleomorphic, hyperchromatic nuclei. Finally the diagnosis of carcinosarcoma (Malignant Mixed Mullerian Tumour) was favoured.

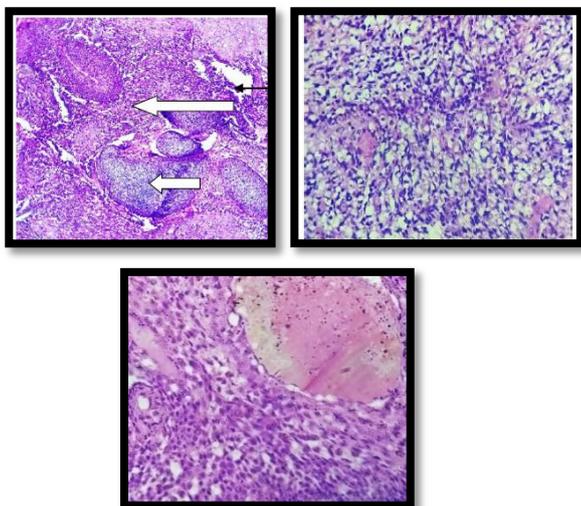


Figure 4: Carcinosarcoma a. Chondromatous element & b. Fibrosarcomatous components c. Epithelial component

E) A 12 years old female came to the outpatient department of Surgery of our hospital, with a history of abdominal pain and gradual increase in the abdominal size for 6-7 months. MRI revealed an evidence

of a huge (22.5x17x 9.5 cm), complex, lobulated mildly T2 hyperintense solid and nonenhancing cystic lesion seen to occupy abdomen and adjacent pelvic cavity, extending from infrapancreatic region above up to the false pelvis below. Multiple foci of calcifications were noted. No intralesional fatty components were seen.

Preoperative tumor markers were high with an alpha fetoprotein (AFP) levels of 171.48 ng/ml, CA125 level of 688.8 U/ml and CEA level of 18.79 ng/ml. Laparotomy revealed a huge left sided ovarian mass, and the omentum and peritoneum of Pouch of Douglas were finely granular. Left sided salpingo oophorectomy was done followed by omentectomy and biopsy of peritoneal implants from Pouch of Douglas and the entire specimen was sent to our Pathology department.

Gross: Left salpingo-oophorectomy specimen showed a well circumscribed, encapsulated, large ovarian tumor, 20 cm in diameter. The tumor was partly solid and partly cystic. The cut surface showed greyish white, bony and cartilaginous areas. The specimen of omentum measured 17 cm in greatest dimension and was greyish white in color. The larger deposit from Pouch measured 2 cm in maximum dimension.

Microscopy: Sections from ovarian mass revealed a tumor composed of ectodermal, mesodermal and endodermal elements. Skin and its appendages, cartilage, bone, muscle tissue, choroid plexus, glial tissue, lymphoid tissue and adipose tissue were present. Majority of the elements was mature. Focal areas of immature mesenchymal elements and neuroepithelial elements were seen. The immature neuroepithelium in the form of rosettes and tubes were present in four low power field and therefore the teratoma was graded as grade 3. The Fallopian tube was free, however, the capsule of ovary was seen to be involved with presence of teratomatous elements just beneath the inked margin.

The omental tissue and the tissue from Pouch of Douglas showed loose textured fibroadipose tissue with sheets and nodules of glial cells along with focal areas of proliferation of mesothelial cells. A diagnosis of immature teratoma (Grade-III) ovary with gliomatosis of omentum and Pouch of Douglas was made.

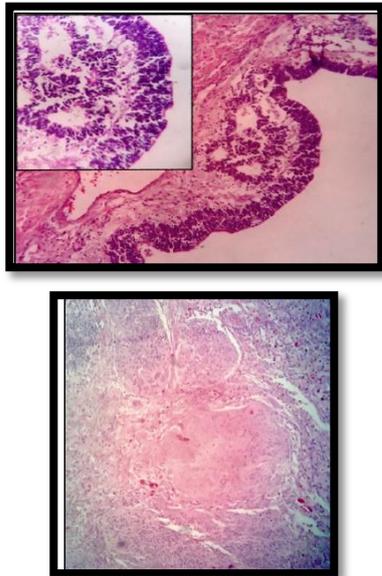


Figure 5: a. Teratoma with immature component
b. Deposit of glial tissue in POD

Discussion

A) Primary ovarian leiomyosarcoma is rare. In particular Epithelioid leiomyosarcoma of ovary is very rare, only one reported case was found before the publication of similar case report in a 42 years nulliparous female by **Bouie S M et al.**⁽⁴⁾ Leiomyosarcoma arises in a median age group of 54 years, de novo and epidemiological studies suggest a role of unopposed estrogen stimulation behind its pathogenesis.⁽¹⁾ Being the most common uterine sarcoma it accounts for 1-2% of all uterine malignancies.⁽²⁾

Unlike leiomyoma, grossly they are fleshy with necrotic and haemorrhagic areas and show signs of invasion. Microscopically typical leiomyosarcomas are hypercellular with prominent nuclear atypia and pleomorphism, mitotically highly active with abnormal mitotic figures and contains areas of structural necrosis.

Apart from the conventional variant, a myxoid form and an epithelioid variant, latter especially notorious for hiding its true mesenchymal nature have been described.

Uterine sarcomas may spread via direct invasion, transtubal transport and lymphatic or hematogenous dissemination. Metastasis occurs in large number of patients (81%) most commonly to the lungs (74%), peritoneum (41%), bones(33%) and Liver (27%).⁽³⁾ ovarian metastasis is less common. **Alvarado Gay and vaga Silva**⁽⁵⁾ described a similar case like ours -an uterine leiomyosarcoma presenting with right sided uterine mass extending into the same sided fallopian tube and ovary, involving ovarian serosa. In case of Transtubal transport of exfoliated cells to the ovaries, peritoneal and pelvic washings may be positive for malignant cells in addition to ovarian serosal involvement. **Dandapani et al** reported a case of uterine leiomyosarcoma metastatic to bilateral ovarian stroma without capsular involvement, which suggests spread by hematogenous dissemination.⁽³⁾

Immunohistochemical techniques can be a useful adjunct in confirming a case of leiomyosarcoma particularly of epithelioid morphology. Consistent immunoreactivity is found for vimentin, smooth and common muscle actin, desmin, calponin and h-caldesmon; although reactivity for low molecular weight cytokeratin (CAM 5.2) and epithelial membrane antigen (EMA) can sometimes further complicate the matter. Estrogen and progesterone receptors are also expressed albeit show lesser intensity than leiomyoma.

Complex numerical and structural chromosomal abnormalities, a hall mark of genomic instability is the rule in case of uterine leiomyosarcomas.⁽²⁾ Overexpression of c-myc, MDM2 and recently identified deletion of p16 tumour suppressor- have all been implicated in neoplastic transformation of the smooth muscle cells.

Prognosis is invariably poor in cases of ovarian leiomyosarcoma; only 2 of the 16 reported cases have survived for 4 and 7 years after adjuvant chemoradiation in the reported case series by

Shakfeh and Woodruff.⁽⁶⁾ Our Patient is currently undergoing chemo radiation.

B) Simultaneous presence of foci of serous carcinoma in ovaries and endometrium pose awesome concern regarding identification of the primary one or considering both being synchronous in nature. Synchronous ovarian and endometrial s carcinoma is rare but it accounts for 50-70% of synchronous cancers of female genital tract. **Makris et al** reported three cases of endometrioid subtype.⁽⁸⁾ A case of synchronous serous carcinoma involving ovaries and endometrium was published by **Sehgal et al**⁽⁹⁾

High grade carcinomas involving bilateral ovaries as well as endometrium can create certain problems ascertaining its type- either endometrioid or serous; based on morphological basis only. villoglandular pattern of endometrioid carcinoma can mimic a serous carcinoma conversely predominant tubuloglandular arrangement in case of serous carcinoma can cause confusion with endometrioid cancer. consistent high grade nuclear features as well as scalloped or frayed luminal margin (lack of common apical margins) can be a important clue in providing a diagnosis in favour of serous carcinoma in such situations.

Mutated p 53 as evidenced by either strong diffuse nuclear staining of p53 or by its complete absence can be a strong corroborative evidence of serous carcinoma (especially differentiating it from high grade endometrioid carcinoma which morphologically can contain ambiguous areas with serous features) it tells nothing about the primary origin. Nuclear expression of WT1 can be a useful marker in this case as endometrial serous carcinomas are usually negative.

p 53 mutations are found in most of the cases of high grade serous carcinoma of ovary along with germline (15-20%) or somatic inactivation of BRCA1 and BRCA2 genes almost in half.⁽²⁾ Now-a -days low grade serous carcinoma is emerging

as quite distinct from this type of tumours being frequently associated with KRAS and BRAF mutations and arising from precursor borderline lesions. It is now well established that most extra uterine high grade serous carcinoma arise from the fimbrial end of fallopian tube from a precursor lesion known as Serous tubal intraepithelial neoplasms or STICs.⁽²⁾

C) Prevalence of Secondary tumours in ovary varies from 3-15% in western countries to 21-30% in eastern population and often presents with the primary remaining occult.⁽²⁾ Secondary involvement by Adenocarcinoma commonly occurs from colorectum, stomach, appendix and breast. Pancreatico biliary primay is uncommon.

In case of presence of signet ring morphology (popularly known as krukentberg tumour) the identification as metastatic deposit is usually straight forward. Other patterns can cause diagnostic difficulties in excluding an ovarian primary especially when these secondaries are large, unilateral and cystic in nature. Infiltrative or nodular growth pattern rather than a confluent glandular one, stromal desmoplasia, involvement of surface and superficial cortex, lymphovascular space involvement in the hilar vessels usually point towards a secondary tumour.⁽²⁾ Presence of dysplasia or atypical proliferative lesions in the ovary can make the thing more complex.

In our case we found that the gall bladder was uniformly and circumferentially involved by adenocarcinoma arising from dysplatic mucosa infiltrating the muscular layer and breaching serosa at multiple places where as ovarian involvement was more suggestive of a secondary. So a primary origin of the tumour in the gall bladder emerged as the most probable diagnosis. **Yaswant kumar et al** reported two similar cases like ours where occult gall bladder cancer has spread to bilateral ovaries with predominant cystic changes causing confusion of primary ovarian tumour.⁽¹⁰⁾ **Young RH et al** published report of six cases of ovarian secondary of biliary tract neoplasm one of which caused significant

diagnostic dilemma due to presence of large cystic component full of mucinous material.⁽¹¹⁾

Immunohistochemistry with CK7, CK20 and Dpc4 can help in categorization in case of a gastrointestinal primary.⁽²⁾ CK7 and CK 20 positivity usually seen in secondaries of pancreatobiliary origin in contrast to colorectal or appendiceal neoplasm, but the same thing can occur in case of gastric secondary and importantly in ovarian primary also. However negativity of Dpc4 is relatively specific for pancreatobiliary origin though it is seen in nearly 50% of cases.

D) Carcinosarcoma of the uterus (malignant mixedmullerian tumors) is a rare occurrence, with an estimated annual incidence of 0.82/100,000 worldwide, and accounts for 2-4% of uterine tumor. It can occur in uterus, fallopian tubes, ovaries.

Carcinosarcoma is, however, highly aggressive, and is composed of epithelial and mesenchymal elements. The epithelial component of a carcinosarcoma may be any type of mullerian carcinoma: mucinous, squamous, endometrioid, high-gradeserous, clear cell, undifferentiated, or mixtures of these types. The endometrioid type is the most common. The stromal components may be homologous (leiomyosarcoma, stromal sarcoma, fibrosarcoma) or heterologous (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, liposarcoma).

Malignant neoplasm of uterus containing both carcinomatous and sarcomatous elements are designated in the World Health Organisation (WHO) classification as carcinosarcomas. In 1899, Gebhardt appears to have reported the first case; Meyer, after a personal examination of the slides, accepted it as authentic.⁽¹²⁾

Carcinosarcomas representing less than 5% of all uterine tumors, account for 16.4% of all deaths caused by a uterine malignancy. There is typically an intimate admixture of high grade malignant neoplasm of epithelium and mesenchyme; one or the other may predominate. The two components are usually distinct and sharply demarcated but

merging can be observed. The epithelium is most often of endometrioid or serous types but other Mullerian types may be encountered. The mesenchymal component, is, for the most part, a high grade, non-specific sarcoma, but heterologous elements including rhabdomyosarcoma, chondrosarcoma and rarely, osteosarcoma are seen in 50% of cases. (WHO2016)

Immunohistochemical and cytogenetic studies show both the epithelial and mesenchymal component arise from a common precursor cell.⁽¹³⁾⁽¹⁴⁾ It is a tumor predominantly identified at the postmenopausal woman, but it can also be found at young women or children.⁽¹⁵⁾

The clinical manifestations are non-specific. Macroscopically, it has a polypoid appearance and of soft consistency, variable color with areas of necrosis and hemorrhage.

Immunohistochemically carcinosarcomas express epithelial markers like Epithelial Membrane Antigen (EMA), pancytokeratin and stromal lineage markers like desmin or S100.

These tumours are associated with a poor outcome and have a pattern of spread similar to high grade endometrial carcinoma. Metastatic spread is typically to pelvic and para-aortic lymph nodes, sometimes with distant haematogenous metastases to lung, brain and bone. However most of the patients die as a consequence of local pelvic/abdominal recurrences. The presence of heterologous elements is a statistically significant poor prognostic factor in stage I disease (WHO2016).⁽²⁾

While hysterectomy with bilateral salpingoophorectomy remains the mainstay of treatment. Recurrences occur in over half of patients after surgical treatment; high rates of recurrences and metastasis suggest a need for lymphadenectomy and post operative adjuvant treatment.

E) Immature teratoma is composed of a mixture of embryonal and adult tissues derived from all three germ layers, regardless of its gross appearance. The

main immature component is usually neuroepithelial, but mesodermal elements are also common.

In patients with extra ovarian spread, the microscopic appearance of the metastasis is of prognostic importance. These implants are usually composed partly or completely of mature glial tissue (gliomatosis peritonei).

According to World Health Organisation, immature teratoma is defined as a teratoma containing a variable amount of immature, embryonal type (generally immature neuroectodermal) tissue. The great majority of teratomas are composed of tissues representing at least two, but usually all three embryonic layers.

Immature teratomas are the third most common of the primitive germ cell tumors, accounting for almost 20% of all cases and 10% to 20% of cases encountered in the first two decades of life.⁽¹⁶⁾

Immature teratomas of ovary are almost always unilateral and occasionally have elevated serum AFP levels like the case presented here. Grossly the cut surfaces are predominantly solid in most cases, but small cysts containing mucinous, serous, or bloody fluid, or hair are frequently present. The immature, embryonic-type tissue composed of neuroectodermal elements like neuroepithelial rosettes and tubules, cellular foci of mitotically active glia, and, occasionally, small areas resembling glioblastoma multiforme or neuroblastoma. It is noted that the amount of neuroepithelium correlates with survival and is the basis of grading these tumors. The only type of neural tissue that should be counted in grading a tumor for immaturity is primitive neural tubes and immature rosettes.⁽¹⁷⁾ In our case, the immature neuroepithelium is represented in the form of rosettes and tubes and were present in 4 lpf and therefore a diagnosis of Grade 3 was given.

Diagnosis of recurrence of immature teratoma by tumor markers appear to be more sensitive when combined with detection of CA 125, CA 153 and AFP. Gliomatosis peritonei is a rare occurrence and has been found exclusively in females with ovarian teratoma (immature and rarely in mature),

though there are stray reports of its association with pregnancy and ventriculoperitoneal shunts performed for hydrocephalus.

The mechanism of implantation is unknown and two hypotheses to explain the origin of gliomatosis peritonei have been proposed. The first One suggests that glial foci arise from primary teratoma through rupture of capsule with subsequent implantation in peritoneum and the second hypothesis suggested that glial foci are genetically unrelated and pluripotent stem cells in the peritoneum or adjacent mesenchyme undergo glial metaplasia.

According to two defining criteria of gliomatosis peritonei proposed by Thulrbeck and Scully,⁽¹⁸⁾ it should be composed of entirely mature glial tissue. Other cases where immature glial implants were found should be diagnosed as metastatic teratoma and require further aggressive therapy. Immature teratomas are treated based on FIGO staging and grading of tumor. Since this is a tumor primarily occurring in young patients, preservation of fertility is an important factor in its management. Grade 1 and FIGO Stage 1 are usually treated with unilateral oophorectomy⁽¹⁹⁾⁽²⁰⁾. Grade II and III with advanced stage receive adjuvant chemotherapy in addition to surgery. Our present case was diagnosed with Grade III immature teratoma and hence was referred to the Oncology department for adjuvant chemotherapy. She has received 6 cycles of treatment with Bleomycin/Etoposide/Cisplatin. At present the patient is being called for follow up every 6 months and she is doing well without any evidence of any residual disease or recurrence.

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