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BRENNER TUMOR -AN OVERVIEW

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INTRODUCTION

The ovaries are an essential part of the reproductive system to produce ovum which helps to regulate hormones and play a prime role in pregnancy and fertility in women health. In contrast, Excess growth of abnormal tissue in any part of ovaries affect the normal reproductive function among women. Generally, Ovarian tumors are prevalent forms of neoplasm among women and it attributes for about 30% of female reproductive cancers. Ovarian cancer is the one of the most habitual female carcinomas, and the fourth main cause of death among cancer demise in female. These tumors act in different ways, and predominantly they are discovered after procuring a bigger volume. There are four major groups of ovarian cancer which are surface epithelial, sex cord or stromal, germ cell and metastatic tumors. Brenner tumor is one of the subtypes of surface epithelial carcinoma which resembles transitional neoplasm of urinary tract.

Eponym

Transitional cell tumors of the ovary, illustrated for the first time by Macnaughton Jones in (1889) and German surgeon "Fritz Brenner" (1877-1969) who characterized it in 1907, are unusual carcinoma and account for about 2% of all ovarian tumors are familiar forms of neoplasia in female. The word Brenner tumor was initially used by "Robert Meyer" in 1932. Brenner tumor of the ovary is a comparatively infrequent neoplasm.

Definition

A smooth, solid or cystic fibro epithelial tumor usually found in the ovaries but can also be found in the adnexal region and the kidneys. It consists of a fibrous stroma with nest of epithelial cells that sometimes resembles the transitional cells lining the urinary bladder.

Brenner Tumor Classifications

According to the "World Health Organization" (WHO) 2003, Brenner tumors classified into three categories:

1. Benign
2. Borderline (atypical proliferative) or low malignant
3. Malignant

Benign Brenner tumors consists of nests of mature transitional-like epithelial cells, which are surrounded by an abundant fibromatous stroma.

Benign tumors are non-cancerous growth. They usually grow slowly and do not spread to other tissues.

Atypical proliferative or Borderline Brenner tumors are characterized by large, irregularly shaped nests, and masses of similar appearing epithelium surrounded by dense fibromatous tissue. Some are made of complex fibrovascular papillae or cauliflower like papillomatous masses, extended beyond into cystic spaces.

Atypical proliferative Brenner tumors are usually related with a benign Brenner tumor. Borderline tumor are abnormal cells that form in the tissue covering the ovary, and they are not cancer which usually cured with surgery.

Malignant Brenner tumors are characterized by cytologic atypia and stromal invasion in a context of a benign or atypical proliferative Brenner tumor. Metastasis to bone, liver, spine, sacrum, iliac, pubic bone etc. Malignant tumors are cancerous and can develop slowly or promptly.

Important: -

There is a distinction between borderline and malignant tumor is the presence of invasion occur in malignancy.

Incidence

Most Brenner tumors (95%) are not cancerous and are called benign which usually occur in women between the age of 30-70 years.

About 5% of Brenner tumors are cancerous (malignant) or have a small chance of spreading beyond its original location called borderline carcinoma which predominantly occurs in the age group of 45-65 years.

Risk factors

Non-Modifiable Factors

1. Brenner tumors most frequently occur in post-menopausal women.
2. Gene associated with ovarian Brenner cancer is UPK3A (Uroplakin3A). Cytoskeletal signaling and keratinization are among its related pathways or super pathways.
3. Women who have a family history of Ovarian cancer is at an increased risk of Brenner tumor especially First-degree relatives such as mother, sister or daughter.

Modifiable Factors

4. Women who consume high meat and low vegetables.
5. Common risk factor is advanced age for most cancers and Brenner tumor is not an exception.
6. Overweight
7. Alcohol and smoking habits.

Etiology

- Unknown
- Brenner Tumor caused by inherited gene mutations or changes.

Clinical manifestation

- Brenner tumor is an incidental finding.
- Benign tumors are mostly asymptomatic unless the tumor is big in size.

If tumor or mass is large,

- Abdominal pain and abdominal swelling.
- Difficulty with bladder control (urinary retention).
- May present with Palpable pelvic mass, discomfort and pain.
- Active tumors mimic sign of hyper Esteronism such as abnormal uterine bleeding or endometrial bleeding.
- Metastatic tumor sometimes presents with "Meigs syndrome" when benign tumors is associated with either sided hydrothorax ascites and other GI Disturbances.
- Generally benign tumor is unilateral whereas rarely reported bilateral.

Diagnostic evaluation

History collection - obtain history about age, family history, comorbid history any long-term complaints such as abdominal pain, discomfort, post-menopausal bleeding etc.

Physical examination- Identify or feel any lump, mass or tenderness while pressing gently on outside of abdomen in lying down position. Identify by accident during surgery such as laparotomy for some reason (or) during a routine pelvic examination and or abdominal palpation.

Routine pelvic examination - Position in dorsal recumbent. Prepare for speculum examination in a sterile manner. Physician can examine by inserting two gloved fingers of dominant hand into vagina, with non-dominant hand pressing down on abdomen. May feel any swollen or lump in reproductive system if abnormal tissue growth or tumor.

Pelvic Ultrasound scan - To detect pelvic mass, mainly hypoechoic solid mass and sometimes calcification may also present in borderline or invasively malignant Brenner tumor. May feel tender mass during scan.

Type of mass at scan may be unilocular, multilocular, unilocular-solid, multilocular- solid and/ or solid.

If presence of Cystic fluid, echogenicity is either anechoic or low
May be no cystic fluid, anechoic, low level, ground glass, hemorrhagic or mixed.

May present with acoustic shadowing, fluid in pouch of Douglas (rare) ascites, papillations, and /or irregular internal wall.

Doppler Ultrasound gives rapid assessment of tissue vascularity.
Benign tumor -either no or minimal blood flow on doppler.

Blood Test

Routine blood investigation such as CBC, Coagulation profile, LFT, RFT, LDH.

If plan for surgery, keep ready crossmatching.
Tumor markers to detect Epithelial Ovarian cancer
CA-125 (normal is <46U/mL)
Sometimes Negative for benign BT

Strongly Positive for Malignant BT & weakly positive for borderline Brenner tumor.

If (Cancer Antigen) CA-125 is normal or Negative with symptoms,

- *CA 72-4* (Cancer Antigen 72-4, Normal 0-6.5ng/ml) to detect Ovarian and Gastric Cancer to confirm metastasis.
- *SCCAg* (Squamous Cell Carcinoma Antigen, Normal:1.5-3ng/mL). It is present in normal epithelium and epithelial tissues.

Other Tumor Markers

- *CA 19-9* (Negative If less than 37U/mL)
  Elevated Carbohydrate Antigen 19-9 in ovarian tumor.

- *CEA* (Carcinoembryonic Antigen) - (normal < 3ng/ ml).
  Increased value to detect mucinous ovarian cancer.

- *AFP* (Alpha Feto Protein) (Normal: 10-20 ng/mL)
  High value to detect endo-dermal sinus tumor and embryonal carcinoma.

- ***Genetic test*** used to detect gene mutations especially UPK3A (Uroplakin3A). Sometimes perform for family members with high risk of ovarian cancer.

Immuno histochemical profile

Malignant Brenner tumor

- Positive for P63 (Tumor protein 63) gene, CK7 (cytokeratin 7), GATA3, uroplakin, EMA (epithelial membrane antigen), S-100 (Schwannian tumor mark-100) protein, thrombomodulin, WT1 (Wilms' tumor suppressor gene1)
- Negative or only weakly positive for Ck20.

Surgical Biopsy

- Confirmed diagnosis is made by microscopic exam of piece of tumor obtained by surgical biopsy.
- Collect sample of biopsy and store in 4% paraformaldehyde solutions and send for Histopathological Examination.
- Histological report or result according to some parameters such as Gross configuration (solid or cystic), Tumor size (in centimeters), Gross tumor color, Microscopic calcification

Macroscopic appearance

Benign Brenner Tumor- Typically small solid tumors measures around 2-8cm in diameter.

- Calcification may present
- Rarely very extensive.
- Papillary projection less common.
- Infrequent but predominately cystic, but small cysts are often seen in solid tumor.
- Expression of p63 protein is limited

Borderline and malignant Brenner Tumor

- Typically, larger than benign.
- Measuring up to 30cm.
- Cystic with solid papillary projections (cysts contain watery or mucous substance.)

Malignant Brenner Tumor

- Sometimes necrotic and hemorrhagic.

Microscopic appearance

Benign Brenner Tumor

- Shows epithelial cell nests growing in a fibrous stroma. (Fig 1.A)
- Coffee bean nuclei common. (Fig 1.B)
- Expression of p63 protein is less limited.

Borderline Brenner Tumor

- Show complex architecture with branching papillae covered by urothelial looking cells.
- May have mitoses.
- No stromal invasion of malignant calls.
- Expression of p63 protein is limited

Malignant Brenner Tumor

- Presence of invasive epithelial cells in associated with benign or borderline Brenner tumor.
- Presence of cystic structures with occasional papillary structures.
- Less fibrous tissue.

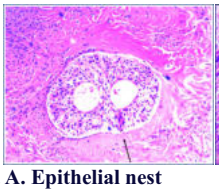

Fig 1. A. Epithelial nest exhibited in the center and light pink stained objects inside the lumen

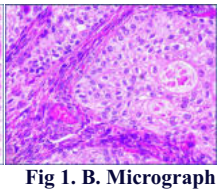

Fig 1. B. Micrograph Coffee bean nuclei with central longitudinal grooves.

Computer tomography Scan with contrast

- Shows the location (left or right side), size (mean diameter of the three planes), shape (round, oval or lobulated), boundary (clear or obscure), components of mass (solid, cystic or mixed), CT density, MRI signal intensity, and ascites in the abdomen and pelvis.
- Visibility of amorphous and/ or multiple, scattered calcification in solid or cystic mass with mild or moderate enhancement.

Magnetic Resonance Imaging

- The dense fibrous stroma demonstrates lower signal intensity to that of a fibroma on T2-weighted sequences imaging.
- May present with Extensive amorphous calcification is often within the solid component. (Fig 2.A)

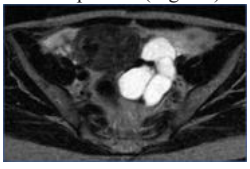

Fig 2. A. MRI findings shows extensive amorphous calcification in Brenner Tumor.

18F-fluorodeoxyglucose positron emission tomography (FDG-PET)

- The F-18 FDG is injected into the patient before scan.
- The PET scanner detects the radiation emitted from the patient, and the computer generates three-dimensional images of tissue function or cell activity in the tissues of the body.
- Helps to Show FDG uptake and calcification in the solid, cystic or mixed component.
- Mild or moderate FDG uptake according to type of Brenner tumor.

Important: -
Perform all diagnostic test before and after surgery to know the effectiveness of medical and surgical treatment.

Differential diagnosis
General imaging differential considerations include:
1. Ovarian fibroma
2. Ovarian fibrothecoma
3. Cystoadenocarcinoma
4. Krukenberg tumor
5. Leiomyomas.

Ovarian Fibroma presents as a homogeneous solid mass with a smooth border and minimal enhancement, but occasionally involves cystic changes and necrosis calcification.

Ovarian Fibrothecoma presents as a round, oval or lobulated solid tumors that cast stripy shadows and are associated with fluid in the pouch of Douglas, and most manifest minimal to moderate vascularization.

Cystoadenocarcinoma presents as an adnexal cystic-solid mass with an unclear border and cystic-solid borderline, an unequally thickened cystic wall with multiple nodules and septa and is usually accompanied by peritoneal lumen implantation metastasis.

Krukenberg tumors are usually bilateral with additional findings of primary malignancy, and frequently accompanied by abdominal and pelvic effusion or metastasis.

Leiomyomas present with a limited amount of dot- or eggshell-like calcification with a similar degree of enhancement as Brenner tumors Furthermore, the difference of blood supplies may be detected between Brenner tumor and leiomyomas.

Prognosis
The long-term prognosis of
- Benign Brenner tumor ranges from good to excellence.
- Borderline Brenner Tumor appears to be much more favorable.
- Malignant Brenner Tumor is poor due to metastasis within the abdominal cavity and may extend to the pleura, lung, liver, kidneys, skeleton, and urinary bladder.

Treatment
- In some cases, Benign tumors need no treatment.
- Doctors use "Watchful waiting" to make sure they cause no problems.
- If tumor is malignant or benign huge mass, usually surgery is a solution to remove the tumor.
- The option of Surgeries as per extension of tumor mass and preserve fertility for young women.
- Exploratory Laparoscopy to remove tumor if painful or large mass.

For post-menopausal women: -
Total Abdominal hysterectomy and Bilateral Salpingo-Oophorectomy (TAH BSO) - Removal of uterus, Fallopian tube and both ovaries.
Pelvic and para-aortic lymph node dissection – Removal of cancerous tissue growth in periaortic lymph nodes that lie in front of the lumbar vertebrae near aorta, in metastasis.
Omentectomy- Remove omentum, which is a thin fold of abdominal tissue that encases the stomach, large intestine and other abdominal organs for cancerous tissue growth invaded omentum.

Post-operative treatment
- After surgery, start adjuvant chemotherapy courses as per oncologist.
- Preferably the first line chemotherapy for the most cases.
- Intravenous chemo with paclitaxel and carboplatin every 21 days up to 6-7 cycles according to extension of tumor.

Recurrent tumor
In case of recurrent growth of tumor after first line treatment, consult with oncologist regarding second line chemotherapy with radiation as a palliative therapy to control following recurrence. Preferably combination chemotherapy such as Gemcitabine, Tamoxifen, Doxorubicin.

Diet Management
Consume healthy food to enrich ovarian function, promote healthy ovarian tissues and fight or prevent cancer.

Vitamin A Rich food
- Plays an important role in ovarian health.
- Helps ovaries begin meiosis which is type of cell growth used to produce eggs.
- Fight ovarian cancer growth.
- Recommended Vitamin A intake is 2300 international units per day for women.
- Vitamin A rich foods include Cod liver oil, eggs, milk, sweet potatoes, carrots, kale, spinach and pumpkin and seeds.

Selenium Rich food
- Selenium is an essential mineral for healthy ovaries.
- Selenium activates glutathione peroxidases & act as antioxidants.
- It protects ovary tissues from oxidative damage, which increases the risk of genetic mutations associated to cause cancer.
- It also activates another protein, called Sep15 (Selena protein-15 gene), that fights cancer development which leads to lower risk of ovarian cancer.
- Recommended selenium daily intake is 55 mg for women.
- Selenium rich foods include Whole-wheat bread, Brazil nuts, meats, eggs and shellfish etc.

Vitamin C Rich Food
- Vitamin C naturally enrich protection against ovarian cancer.
- Vitamin C activates immune cells, called natural killer cells that attack growth of cancer cells and tissue.
- Adequate vitamin C promotes healthy ovarian function by regulating the activity of genes needed for follicle development.
- Recommended daily intake of vitamin C-75mg.
- Vitamin C rich foods include oranges, Strawberries, red peppers and broccoli

Prevention
- Stop tobacco and alcohol intake.
- Maintain Regular physical activity, healthy body weight, and healthy rich diet enhance healthy ovaries.
- Regular screening for cancer after menopause especially routine blood investigation with tumor marker CA 125, Scan, CT etc.
- Avoid excessive radiation exposure such as Ultraviolet (UV rays) is a particular solar radiation which carries carcinogenic agent and so that use sunscreen and protective clothing are effective preventive measures.
- Genetic counseling because Brenner tumor is sometimes associated with a gene mutation that can be inherited in families.
- Risk reducing surgeries such as oophorectomy (removal of healthy ovaries to reduce the chance to grow the tumor tissues).

CONCLUSION
Brenner tumors are commonly asymptomatic benign neoplasms of the ovary, which are perpetually diagnosed unexpectedly amid surgical procedures. They are mostly observed in the postmenopausal period with vaginal bleeding and can be synchronized with other ovarian pathologies and female genital tumors. Brenner tumors need further intervention trials and studies in order to obtain enough reviews for future research and evidence-based practices.

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