Ovarian Pathology

NON-NEOPLASTIC CYSTS

Normally follicles and corpus luteum do not exceed a diameter of 2 cm (and called cystic follicle). When their diameter is greater than 3 cm, they are termed as *follicular cyst*.

Follicular cysts

Are frequently multiple, filled with clear serous fluid and may attain a diameter up to 8 cm. When large, they produce clinical symptoms.
Microscopy: They are lined by granulosa cells. pressure may cause atrophy of these cells.

Luteal cysts

Are formed by rupture and sealing of corpus haemorrhagicum. The wall of these cysts is composed of yellowish luteal tissue (lutein = yellow pigment).
Microscopy: Luteal cysts are commonly lined by luteinized granulosa cells.

Polycystic Ovary Disease (Stein-Leventhal Syndrome)

Is a complex endocrine disorder characterized by hyperandrogenism, menstrual abnormalities, polycystic ovaries, chronic anovulation, and decreased fertility. It usually comes to attention after menarche in teenage girls or young adults who present with oligomenorrhea, hirsutism, infertility, and sometimes with obesity.
Pathogenesis: The etiology of PCOS remains incompletely understood, in most patients, the principal biochemical abnormalities are excessive production of androgens, high concentrations of LH, and low concentrations of FSH. It is proposed that the ovaries elaborate excess androgens, which are converted to estrogenic hormones in peripheral fatty depots, which inhibit the secretion of follicle-stimulating hormone by the pituitary through the hypothalamus.
Morphology:
Grossly: The ovaries are usually involved bilaterally and are at least twice the size of the normal ovary. They are grey-white in color and studded with multiple small (0.5-1.5 cm in diameter) bluish cysts just beneath the cortex.
Microscopy: The outer cortex is thick and fibrous. The subcortical cysts are lined by prominent luteinized theca cells and represent follicles in various stages of maturation but there is no evidence of corpus luteum.

OVARIAN TUMORS

Ovarian tumors are relatively common, approximately 80% being benign and occurring in women of reproductive age. Malignant tumors occur in older women, most commonly aged 40–65 years, although certain uncommon tumor types do occur at a younger age.
Many ovarian tumors – particularly of epithelial type – are bilateral.
Most ovarian tumors are non-functional and, in view of their hidden anatomical location, tend to present late (that is why the prognosis of malignant ovarian tumors are mostly grim), usually as abdominal swelling due to the presence of a mass or associated ascites.
Tumors of the ovary are amazingly diverse pathologic entities. This diversity is attributable to the three cell types that make up the normal ovary: ***the surface (coelomic) covering epithelium***, the ***totipotential germ cells***, and the ***sex cord/stromal cells***. Each of these cell types gives rise to a variety of tumors.

1- SURFACE EPITHELIAL TUMORS

These neoplasms are derived from the coelomic mesothelium that covers the surface of the ovary. With repeated ovulation and scarring the surface epithelium is pulled into the cortex of the ovary, forming small epithelial cysts also called (inclusion cyst), the lining epithelium of this cyst can undergo metaplasia and neoplastic transformation into epithelial tumors of the various histologic types. Benign lesions are usually cystic (cystadenoma). Malignant tumors may also be cystic (cystadenocarcinoma) or solid (carcinoma). The surface epithelial tumors also have an intermediate, borderline category currently referred to as *tumors of low malignant potential* (borderline tumors), the majority of borderline tumors behave in a benign manner they can recur and some can progress to carcinoma thus, they have a better prognosis than the fully malignant ovarian carcinomas.

Several risk factors for epithelial ovarian cancers have been recognized include: nulliparity and family history. There is a higher incidence of carcinoma in unmarried women and married women with low parity. Interestingly, prolonged use of oral contraceptives reduces the risk somewhat. there is increased risk for ovarian cancers when there are mutations in *BRCA1* and *BRCA2* genes, the average lifetime risk for ovarian cancer approximates 30% in *BRCA1* carriers, the risk in BRCA2 carriers is somewhat lower.

A- Serous Tumors

These are the most frequent of the ovarian tumors. About 60% are benign, 15% of low malignant potential, and 25% malignant. Combined, borderline and malignant serous tumors are the most common malignant ovarian tumors and account for about 60% of all ovarian cancers**.**

The prognosis for the individual with invasive serous cystadenocarcinoma after surgery, radiation, and chemotherapy, is **poor** and depends heavily on the **stage of the disease** at the time of diagnosis.

Morphology

Grossly, most are large, spherical to ovoid, cystic structures, as large as 30 to 40 cm in diameter. In the benign form, the serosal covering is smooth and glistening. In contrast, the surface of the cystadenocarcinoma shows nodular irregularities, on transection, the small cystic tumor may reveal a single cavity, but larger ones are usually divided by multiple septa into a multiloculated mass. The cystic spaces are usually filled with a clear serous fluid, polypoid or papillary projections into the cyst cavity may seen, which become more marked in malignant tumors**.**

Histologically, the benign tumors are characterized by a single layer of tall columnar epithelium that lines the cyst. The cells are in part ciliated.

Frank carcinoma characterize by anaplasia of the lining cells with invasion of the stroma. Papillary formations are complex and multilayered. Psammoma bodies (concentrically laminated calcified concretions) are common in the tips of papillae.

Malignant serous tumors spread throughout the peritoneal cavity and to regional lymph nodes, including periaortic lymph nodes; distant lymphatic and hematogenous metastases are infrequent.

Between these benign and obviously malignant forms are the tumors of low malignant potential (borderline tumors) which characterize by milder cytological atypia than frank carcinoma and **NO** stromal invasion.

B- Mucinous tumors

Consists of mucin-secreting cells. These tumors are considerably less likely to be malignant than serous tumors, accounting for about 10% of all ovarian cancers. Only 10% of mucinous tumors are malignant *(cystadenocarcinomas),* while 10% are borderline, and 80% are benign. The prognosis of mucinous cystadenocarcinoma is somewhat better than that for the serous counterpart, but the stage rather than the histologic type is the major determinant of treatment success.

Morphology

Only about 5% of benign and 20% of malignant mucinous tumors are bilateral, a much lower incidence than for their serous counterparts. Bilateral mucinous tumors of the ovary must be differentiated from metastatic adenocarcinomas of the gastrointestinal tract, which may present as ovarian masses.

Grossly: the cyst is larger and multilocular, and papillary formations are less common than serous, serosal penetration, and solidified areas point to malignancy.

Histologically: mucinous tumors are classified according to the character of the mucin-producing epithelial cells. include tumors with endocervical and intestinal-type epithelia. The latter is almost always present in mucinous tumors with borderline tumor and mucinous carcinomas. Malignant tumors are characterized by solid areas of growth, piling up (stratification) of lining cells, cytologic atypia, and stromal invasion.

Rupture of mucinous tumors may result in mucinous deposits in the peritoneum.

C- Endometrioid Tumors

These tumors may be solid or cystic, but sometimes they develop as a mass projecting from the wall of an endometriotic cyst.

Microscopically they are distinguished by the formation of tubular glands, similar to those of the endometrium, within the linings of cystic spaces. Endometrioid tumors are usually malignant.

About 15% - 30% of women with these ovarian tumors have a concomitant endometrial carcinoma. Similar to endometrial cancer, endometrioid carcinomas have mutations in the *PTEN* suppressor gene.

D- Brenner Tumor

The Brenner tumor is an uncommon, solid, usually unilateral ovarian tumor consisting of an abundant stroma containing nests of transitional-like epithelium resembling that of the urinary tract.

Brenner tumors are generally smoothly encapsulated and gray-white on transection and range from a few centimeters to 20 cm in diameter. These tumors may arise from the surface epithelium or from urogenital epithelium trapped within the germinal ridge. These tumors mostly are benign.

2- TUMORS OF GERM-CELL ORIGIN

Around 95% of these tumors are mature cystic teratomas (‘dermoid cysts’). Teratomas constitute 15% to 20% of all ovarian tumors. The immature malignant variant is rare.

Benign (Mature) Cystic Teratomas

Almost all of these neoplasms are marked by differentiation of totipotential germ cells into mature tissues representing all three germ cell layers: ectoderm, endoderm, and mesoderm. Usually there is the formation of a cyst lined by epidermis with adnexal appendages-so called *dermoid cysts.* About 90% are unilateral. On transection, they are often filled with sebaceous secretion and matted hair that, when removed, reveal a hair-bearing epidermal lining . Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or gastrointestinal epithelium, and other recognizable lines of development are also present. In about 1% of cases there is malignant transformation of one of the tissue elements.

Immature Malignant Teratomas

These neoplasms are found early in life, the mean age being 18 years. They differ strikingly from benign mature teratomas insofar as they are often bulky, predominantly solid or near-solid on transection, and are punctuated here and there by areas of necrosis; uncommonly, one of the cystic foci may contain sebaceous secretion, hair, and other features similar to those in the mature teratoma. Microscopically, the distinguishing feature is a variety of immature or barely recognizable areas of differentiation toward cartilage, bone, muscle, nerve, and other structures. Particularly ominous are

foci of neuroepithelial differentiation, because most such lesions are aggressive and metastasize widely.

Specialized Teratomas include

1-Struma ovarii is composed entirely of mature thyroid tissue that, interestingly, may hyperfunction and produce hyperthyroidism. These tumors appear as small, solid, unilateral brown ovarian masses.

2- Ovarian carcinoid, which in rare instances has produced the carcinoid syndrome.

Other germ cell tumors

Dysgerminoma which is the ovarian counterpart of testicular seminoma account for about 2% of ovarian cancers and roughly 50% of malignant ovarian germ cell tumors. About 75% occur in the second and third decades. Some occur in patients with gonadal dysgenesis.

The tumor is radiosensitive. Morphology similar to seminoma of testis.

Yolk sac tumors it ranks as the second most common malignant tumor of germ cell origin. It is thought that to be derived from malignant germ cells that are differentiating along the extraembryonic yolk sac lineage. Its characteristic histologic feature is a glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space that is also lined by tumor cells (Schiller-Duval body).

Embryonal carcinomas are rare and highly malignant tumor of primitive embryonal elements that is histologically similar to embryonal carcinoma arising in the testes.

Choriocarcinomas Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinoma is extremely rare. They are histologically identical to the more common placental lesions. The ovarian tumors are aggressive and have usually metastasized hematogenously to the lungs, liver, bone, and other sites by the time of diagnosis. Like all choriocarcinomas they elaborate high levels of chorionic gonadotropins, which may be helpful in establishing the diagnosis or detecting recurrences. In contrast to choriocarcinomas arising in placental tissue, those arising in the ovary are generally unresponsive to chemotherapy and are often fatal.

3- OVARIAN SEX CORD/STROMAL TUMOURS

These tumors differentiate along female (granulosa and theca cell tumours) or male (Sertoli/ Leydig's cell tumors) lines.

Granulosa cell tumors are fairly common, composed of cells that resemble granulosa cells of a developing ovarian follicle. It is of 2 types adult and juvenile granulosa cell tumors largely based on the age of the patient, the clinical importance of this tumor these lesions behave in a low grade malignant fashion and may secrete estrogens. As a result it associated with endometrial hyperplasia, endometrial carcinoma and proliferative breast disease.

Morphology has many histologic patterns. The small, cuboidal to polygonal cells (coffee bean like) with longitudinal groove may grow in anastomosing cords, sheets, or strands and occasional cases, small, glandlike structures filled with an acidophilic material recall immature follicles (Call-Exner bodies) is diagnostic for this tumor.

4- METASTATIC TUMORS

About 10% of ovarian cancers are secondary carcinomas. The most common metastatic tumors of the ovary are derived from tumors of müllerian origin: the uterus, fallopian tube, contralateral ovary, or pelvic peritoneum.

The most common extra-müllerian tumors metastatic to the ovary are carcinomas of the breast and gastrointestinal tract, including colon, stomach, biliary tract, and pancreas. Metastasis may occur by direct extension from adjacent organs (e.g. uterus, fallopian tube and sigmoid colon) by lymphatic or haematogenous routes.

Bilaterality of the tumor is the most helpful clue to diagnosis of metastatic tumor.

Krukenberg Tumor

Krukenberg tumor is a distinctive bilateral tumor metastatic to the ovaries by transcoelomic spread*. The tumor is generally secondary to a gastric carcinoma but other primary sites where mucinous carcinomas occur (e.g. colon, appendix and breast) may also produce Krukenberg tumor in the ovary. Krukenberg tumor forms rounded or kidney-shaped firm large masses in both ovaries.

Cut section shows grey-white to yellow firm fleshy tumor and may have areas of haemorrhage and necrosis.

Microscopy It is characterized by the presence of mucus-filled signet ring cells which may lie singly or in clusters. It is accompanied by sarcoma-like cellular proliferation of ovarian stroma.

***Transcoelomic** metastasis refers to the dissemination of malignant tumors throughout the surfaces and organs of the abdominal and pelvic cavity covered by peritoneum.