Introduction

In 1929, Taylor first described a subset of epithelial ovarian tumors that he termed semimalignant. These lesions have a more favorable outcome than do other ovarian cancers, but they were not separately classified by the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) until the early 1970s.

The borderline ovarian tumors (BOTs) or atypical proliferative ovarian tumors (APOTs) are of particular importance to the women affected and to gynecologists caring for them as well as to the women's families. They are also important for the pathologists charged with establishing an accurate diagnosis and for the researchers who are trying to explain the tumors' complex pathogenesis.

BOTs or APOTs are of epithelial origin and represent a unique intermediate stage between the benign cystadenomas and the adenocarcinomas. They are separated from cystadenomas by the presence of cellular atypia and from high-grade malignant tumors by the presence of destructive stromal invasion. Some BOTs or APOTs have a minor form of invasion designated as microinvasion; some tumors present small focal areas that exhibit moderate to

severe atypia that are designated as intraepithelial carcinomas. BOTs or APOTs share multiple similarities and differences as demonstrated below **(Acs, 2005 and Karseladze, 2005).**

BOTs or APOTs represent 15–20% of atypical cell proliferations of the ovary **(Scully et al., 1998; Webb et al., 2004; Wong et al., 2007).**

In general, these tumors have an excellent disease-free survival after surgical treatment. BOTs or APOTs have been recognized for more than 70 years; nevertheless, several authors going back to the late 1800s reported ovarian tumors with histological and clinical features between benign cystadenoma and high-grade malignant tumors **(Abel, 1901; Pickel and Tamussino, 2003; Pickel and Reich, 2006).**

The BOTs or APOTs were separated into a new category of neoplastic processes as a result of the observation made by Taylor and others **(Serov, 1973).**

Authors noted that some tumors displaying papillary features and some with tumor deposits on the peritoneal surface had excellent survival, especially those of serous type. However, other tumors with the same stage and somewhat similar histologic architecture were rapidly fatal. The serous cystadenoma can progress to BOTs or APOTs

and finally becomes a serous low-grade carcinoma. These three entities (cystadenoma, BOT or APOT, and low-grade serous carcinoma) are different biologically, in their clinical course and treatment modalities **(Seidman, 2000; Seidaman, 2011).**

In 1971 the Cancer Committee of the International Federation of Gynecology and Obstetrics, proposed a classification of common primary epithelial ovarian tumors. They subdivided the tumors into benign cystadenoma, cystadenoma with proliferative activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth, low malignant potential tumors, and cystadenocarcinoma **(Lee and Prat, 2003).**

Later in 1973, the World Health Organization catalogued tumors with histologic characteristics of carcinoma, but with good behavior as “tumors of borderline malignancy”.

In the WHO classification of 2003, these neoplasms are simply designated as “borderline tumors”; they have been too widely recognized as ovarian tumors of “low malignant potential,” and as “proliferative ovarian tumors," terminology that was accepted by the WHO in the year 2000. At the present time, the use of the designation “low malignant potential” is not recommended. To further

complicate the issue of BOTs or APOTs, the presence of microinvasion has been introduced in the past few decades. Microinvasion may be represented by a single focus or multiple foci of epithelial cells with histologic characteristics identical to those of BOTs or APOTs. The cells forming the focus or foci of microinvasion are seen in the nearby stroma surrounded by an empty space or cleft supposedly filled by serous fluid and without stromal reaction, necrosis or inflammation as illustrated. The empty space could also be the result of tissue retraction. The size of the focus or foci of microinvasion is calculated by using three different scales **(Fritz et al., 2000)**.

Bell and Scully reported that it should not exceed 3 mm in diameter **(Bell and Scully, 1990).**

Later, a 10 mm2area was suggested by others, a 5 mm linear dimension was also suggested and is recommended for all forms of BOTs or APOTs. It is probably the most common dimension used today to calculate microinvasion **(Santesso and Kofumeier, 1968; Bell et al., 2004).**

The 3 mm linear dimension and the 10 mm2 area are arbitrary numbers and have not been scientifically validated **(Silva, 1996; Smith Sehdev et al., 2003)**.

The atypia in BOTs or APOTs is supposed to be of intermediate degree, nevertheless, there are areas of BOTs or APOTs that show changes amounting to small intraepithelial carcinomas (epithelial stratification, loss of polarity, marked nuclear atypia, cribriform architecture, and occasional mitoses) **(Scully, 1999).**

Between 20% and 40% of BOTs or APOTs are associated with extraovarian tumors deposits or implants (implants, concomitant tumor or metastasis). The stromal invasion or non-invasive nature of this tumor deposits is a very important histological parameter to determine the tumor behavior **(Hart et al., 1977; Riman et al., 2001; Modugno, 2001).**

Aim of the Work

Review of outcome of the current therapeutic strategies in wemen with borderline ovarian tumors (fertility & morbidity & recurrence & survival) at the Ain shams gynecological oncology unit over 10 years (2005-2015).

Pathology

Serous borderline ovarian tumors/ atypical proliferative serous tumors/ low-grade serous carcinoma:

The annual incidence of serous borderline ovarian tumors (SBOTs) or atypical proliferative serous ovarian tumors (APSOTs) in the USA is 2.5/100,000 of which 1.5/100,000 occur in white women. Between 1995 and 2004 the incidence rate in Norway and Sweden has been reported as 4.8 per 100.000 women, almost double that of the USA **(Seidman, 2010)**.

Serous borderline ovarian tumors or APSOTs account for 10% of the ovarian serous tumors and 56% of the BOTs or APOTs; the patients have an average age of 46 years; few are found between 12 and 19 years of age and few in the 9th decade. In the series of Longacre et al. 1.4% of the patients were pregnant at the time of diagnosis. The SBOTs or APSOTs occur in slightly older women than do the cystadenomas, but in younger women than those with ovarian invasive carcinoma. The SBOTs or APSOTs are bilateral in 25–37% of the cases. In a more recent series bilateralism was reported as 55% **(Seidman, 2010).**

Gross examination:

On gross inspection, SBOTs or APSOTs are similar to serous cystadenomas and to some adenocarcinomas. The tumors are round, ovoid or irregular in shape with the size ranging from 1 to 35 cm in diameter with a mean of 10.4 cm (Fig. 1). They are reddish, pink or yellowish blue; occasionally exhibiting brown discoloration secondary to intraluminal or intramural hemorrhage. Their external surface may be smooth, sometimes with alternating areas with irregular indurations formed by thick fibrous tissue. The indurate areas are occasionally associated with dystrophic calcification. The lining of the cyst wall can show both, serous and mucinous type epithelium with benign features as seeing in Fig. 2.

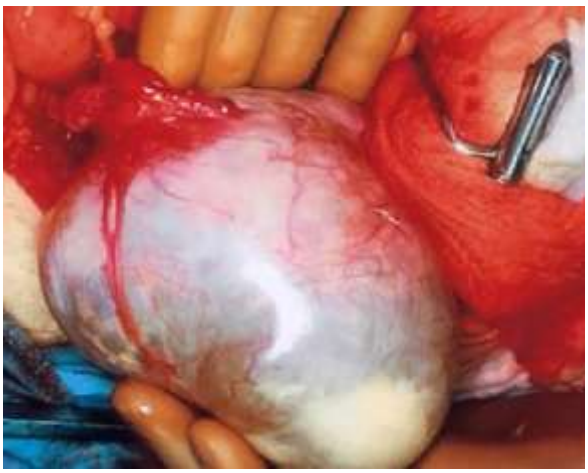

Fig. (1): External surface of a SBOT showing a smooth, tense capsule with prominent vessels and thick fibrous areas. **(Photo courtesy of Dr Richard Stock, 2000)**

Blood vessels in the cyst wall can be very prominent (Fig. 1) depending on the tumor contents they can be translucent; on palpation it can be fluctuant or somewhat firm. On sectioning the tumor, it can be unilocular or multilocular, and may show secondary or "daughter" cysts of varying size and shape.

Small or exuberant papillary structures can be seen on the external surface of the cyst wall, identical to those present in the cyst lumen (Figs. 3 and 4). Frequently the fallopian tube is attached to the cyst wall, and could be quite elongated; sometimes it is embedded in the cyst wall (Figs. 3 and 4). Fibrous adhesions are often seen **(Colgan and Norris, 1983).**

The tumor contents can be a clear straw-colored fluid, hemorrhagic or quite frequently thick mucinous. The mucinous content does not necessarily indicate that the tumor is of mucinous type. The cyst inner lining exhibits arborizing or papillary structures; they can fill the entire lumen or alternate with smooth surfaces (Figs. 3 and 4). The papillary structures are generally yellow-brown or tan in color; they are soft and fragile and are covered by serous, brown or mucinous fluid. The ovary can be difficult to identify, especially when the tumor is very large, it may be reduced just to a thickened part of the cyst wall (Fig. 4).

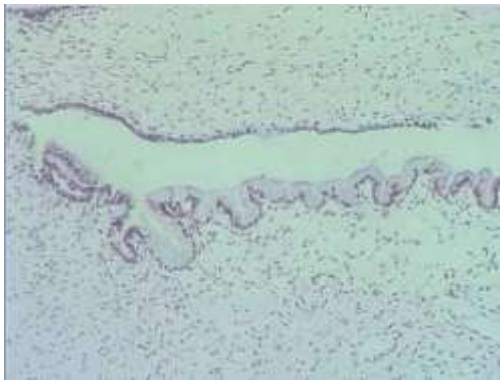

Fig. (2): Section of the wall of a cystadenoma exhibiting two types of epithelia. Low columnar serous type (top) and tall columnar mucinous-type with basally located nuclei (bottom). This mixture of epithelia is found in serous or mucinous ovarian tumors of the ovary **(Colgan and Norris, 1983).**

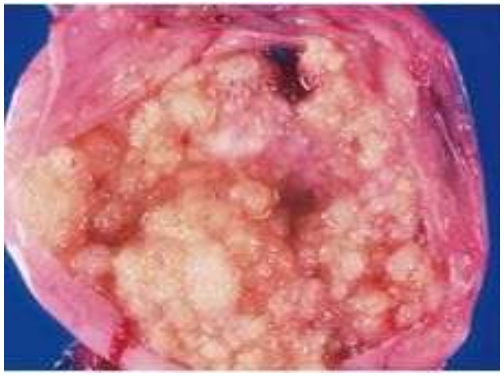

Fig. (3): SBOT or APSOT demonstrating growth of papillary projections arising from the internal surface of the tumor. Bubbly seromucinous fluid is present **(Kurman and Seidman, 2000)**.

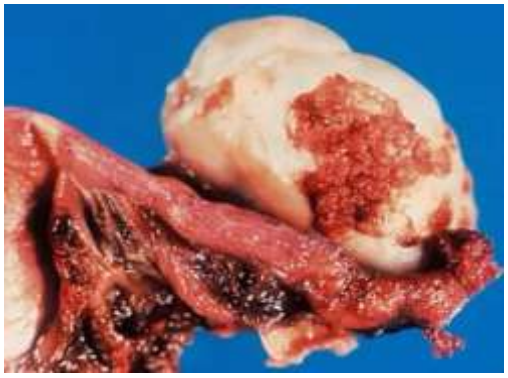

Fig. (4): Adnexal complex exhibiting SBOT or APSOT showing exophytic papillary growth. The comus of the uterus and the Fallopian tubes are seen clearly **(Kurman and Seidman, 2000)**.

SBOTs or APSOTs are associated with peritoneal implants in approximately 40% of the cases, 9% of the implants were invasive and 31% noninvasive **(Kurman and Seidman, 2000).**

A thorough and meticulous examination of the outer and inner lining of the cyst wall by the pathologist is paramount. This exam may occur when the tumor is opened in the frozen section room, or in the gross room, when an intraoperative consultation did not take place. The pathologist should perform or supervize the gross examination and strongly emphasize to the residents, fellows and pathologist assistants, that a thorough gross examination and specimen sampling is very important for the pathologist to generate an accurate final histopathologic interpretation. The thorough gross examination of the tumor impacts on patient outcome.

Microscopic features:

By microscopic examination SBOTs or APSOTs are characterized by the presence of a cyst cavity or complex cystic spaces with infoldings and exuberant hierarchical papillary structures (Figs. 5–7). The papillae can occupy from 10 to 100% of the cyst cavity. In approximately 42% of cases, papillae can be present in both the cyst cavity and on the external surface of the cyst; the presence of papillae on the external surface has been reported in up to 70%.

If there are papillary structures present only on the external surface of the SBOT or APSOT, which is reported in only 2% of the cases, the lesion would be designated as “serous surface papillary borderline tumor” or atypical

proliferating surface serous tumor **(Kurman and Seidman, 2000).**

According to Longacre et al. 69% of the tumors that have an exophytic component are associated with peritoneal implants compared with 16% of those cases where the tumor is only intracystic. Noninvasive and invasive desmoplastic and epithelial peritoneal implants can be present **(Longacre Kempson and Hendrickson, 1993)**.

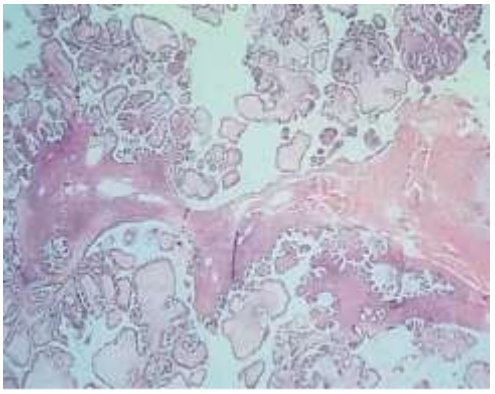

Fig. (5): Photomicrograph of SBOT or APSOT. Observe papillae of different sizes resting on fibrous tissue stroma. Tufting is observed in the interpapillary spaces (hematoxylin and eosin) **(Kurman and Seidman, 2000).**

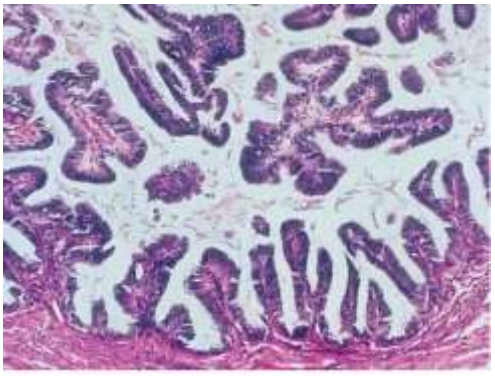

Fig. (6): Inner lining of a serous borderline tumor showing hierarchical papillae with stratification and hyperchromasia. The papillae have fibrous cores. Tufting is seen mixed with fluid in the lumen (hematoxylin and eosin) **(Kurman and Seidman, 2000).**

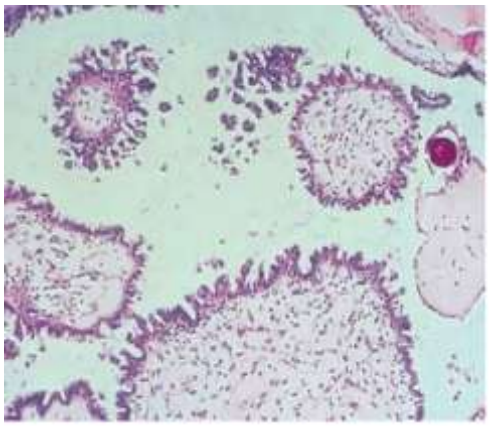

Fig. (7): Photomicrograph of papillae from a serous borderline tumor with edematous stroma, secondary papillary proliferation, and mild inflammatory infiltrate. A small psammoma body is present at the upper right-hand corner associated with a hyalinized papilla (hematoxylin and eosin) **(Kurman and Seidman, 2000).**

The papillae of SBOTs or APSOTs are of multiple lengths, and are branching; they have distinctive edematous, myxoid, or hyalinized connective tissue cores that support the blood vessels. The papillae are lined by different types of epithelia: cuboidal or columnar, tubal (ciliated, clear, and secretory or peg cells), and mucus secreting, either of cervical or enteric types; they usually show an eosinophilic cytoplasm.

The nuclei are round or oval, are located at the base of the cells and show mild to moderate atypia. Some nuclei may be grooved or creased, nucleoli may be apparent; cellular stratification is seen and is one of the most characteristic histologic features of these tumors (Figs. 5, 6, 30 and 31). Psammoma bodies are seen in about 50% of the cases **(Klemi and Nevalainen, 1978; Dietel and Hauptmann, 2000).**

Budding or tufting is very commonly noted as a result of detached groups of epithelial cells from the tips of the papillae, due to lack of connective tissue support. These groups of cells can also form rosette-like structures (Figs. 7 and 9), which are very characteristic of SBOTs or APSOTs.Budding or tufting, often single cells or clusters of cells float in the tumor fluid. Few areas of the tumor lumen or surface may be covered by micropapillae and/or cribriform structures (the result of the fusion of the tips of the papillae, creating the so called roman bridges) that originate on a thick, fibrotic large papillae core.

The micropapillae are filiform, plentiful, and friable, they should not form a confluent area and occupy more that a 5 mm in linear dimension or 10% of the total tumor inner or outer surface, if it does, the lesion is a low-grade papillary serous carcinoma (discussed later). When the tumor is of micropapillary type, the papillae may not show stroma. The nuclei are located at the base of the cells; they are round to oval and show mild or at most moderate atypia. Some nuclei may be grooved or creased; nucleoli may be apparent. Few SBOTs or APSOTs show severe or high-grade atypia; those tumors would be considered of unclear classification and expected to have a more aggressive behavior. **(Dietel and Hauptmann, 2000).**

In a recent publication McCluggage makes the point that the presence of severe nuclear atypia in a serous ovarian lesion, even in the absence of invasion, is sufficient to diagnose the tumor as a high-grade serous carcinoma. Mitotic figures are few and should be typical; probably do not exceed 4 per 10 HPF. Papillary structures present on the external surface of the tumor do not mean that the tumor has penetrated the wall of the cyst; they arise de novo on the ovarian surface epithelium and can be the only component of the tumor **(McCluggage, 2010)**. The presence of epithelium with atypia should encourage the pathologist to go back to the gross specimen, examine it, and submit more sections in order to exclude a possible area of invasion or a frank high-grade invasive serous carcinoma not found in the first inspection. According to some authors, when the severe atypia is only focal (assuming adequate sampling), the pathologist should make a diagnosis of SBOT or APSOT with intraepithelial carcinoma (Fig. 8) **(Scully and Clement, 1998).**

Seidman et al. classified microinvasive carcinoma as a form of microinvasion, which is typified by the presence of small solid nests of cells associated with micropapillae and distributed in a disorganized fashion. The group of cells, that sometimes show a cribriform pattern, are surrounded by a clear space and accompanied by desmoplasia. This resembles primary ovarian invasive low-grade serous carcinoma, or microinvasive carcinoma. It may be a manifestation of a true invasive serous carcinoma **(Seidaman et al., 2011)**.