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Serous borderline ovarian tumors: Where are we now?

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Summary

In the present article we report the revised microscopical features of serous borderline ovarian tumors (S-BOTs) in the context of a long personal experience, drawing parallels with the definitions and issues elaborated at the Borderline Ovarian Tumor Workshop held in August 2003 in Bethesda. In our opinion none of the histopathologic criteria of the primary tumor including micropapillary subtype of the S-BOT can be used yet as a prognostic marker.

The most realistic assumption is that in the clinical course of the S-BOT dynamic transformation of different clones occurs and the process develops simultaneously with multicentric blastomogenesis in the peritoneal cavity. Hence the failure of our efforts to forecast the prognosis of the disease using the microscopical structure of the primary tumor as a point of issue. It is indispensable to control the course of the S-BOTs by performing repeated biopsies at each relapse and modify the treatment schedules according to the microscopic patterns revealed at a given stage of the disease.

Relapses of the S-BOTS may occur up to 50 years later so the patient should be under surveillance especially by a urologist to detect the earliest symptoms of urinary tract obstruction.

Much more attention should be paid to the local intraabdominal administration of drugs and the search for new systemic chemotherapy regimens.

Key words: Serous borderline ovarian tumors; Borderline ovarian tumors; Ovarian cancer.

The problems connected with both diagnosis and proper therapy of borderline ovarian tumors (BOTs) are well known to oncogynaecologists. Still today ardent discussions continue concerning many principal questions such as what morphological criteria should be used to classify the given neoplasms as BOT? Which parameters may serve for prognostication? Is chemotherapy indicated for the treatment of these patients? etc. Considering the problem from a historical aspect, we should state some progress over the last 30 years. Though our understanding of the mechanisms of the disease is still far from satisfactory we have been moving in the right direction and even if we have not gained too much knowledge about BOTs we have at least abandoned some erroneous positions. One of the conceptual steps forward is rejecting the idea of unifying all histogenetical varieties of BOTs into one group. Except for some principal mutual morphological features, their biology, clinical course and treatment modalities are obviously different.

The ovary is not the single organ wherein tumors of uncertain malignant potential arise. However the main factor complicating the detailed histo- and morphogenetical analysis of BOTs as well as all other ovarian neoplasms, the anatomical position of the ovary, which hinders dynamical microscopical study of the preneoplastic and early neoplastic processes cannot as yet be overcome with any modern methodical facilities. Though laparoscopic surgery has to some extent expanded our possibilities and enabled us sometimes to repeatedly examine the surface of the ovary, at present one cannot perform multiple biopsies of ovarian neoplasms, as frequently as cervical CIN or endometrial hyperplasias. As a result, we always see a particular stage of the disease and are unable to establish the cells of its origin or predict further steps of its progression.

One of the main reasons for the absence of unanimity in clinical life with regard to BOTs is the lack of consensus among pathologists themselves [1]. Clinicians cannot properly analyze the material if the majority of terms and notions used by pathologists are contradictory and vary not only from country to country but from one clinic to another. Fortunately, some positive trends have emerged recently such as frequent meetings of pathologists with detailed discussions on BOT morphology. One of the most remarkable events in elaborating a consensus on many principal problems was a Borderline Ovarian Tumor Workshop sponsored by the National Cancer Institute, which was held in August 2003 in Bethesda, MD. The materials from the Workshop [2-5] comprise not only interesting data on all acute problems of clinical pathology of BOTs but thorough analytical and critical comments considering all the different opinions. Of particular importance are the data on the reasons for discrepancies among different authors in general clinics and scientific centers, and the main issue of the workshop decision – to review the large groups of material preferably with long-term follow-up in close contact with clinicians [2].

How can be the present status of BOTs be summed up? Taking into consideration the extremely multifaceted character of the problem, perhaps it is more appropriate to concentrate on the major complex entity – serous borderline tumors – S-BOTs. Terminological problems are common for all nosological entities of BOTs, especially for serous varieties. Indeed the substitution of «borderline» with other words did not add exactitude to our definitions. The most

often-attributed term «atypical proliferative serous tumors» [6] does not seem tenable. First, the proliferation was never proved to be particular to any type of neoplastic cells. All of them are proliferating to some extent or another. There are lots of slow growing, overtly malignant tumors and one can encounter a very high proliferative rate in benign tumors or tumor-like lesions as well. The adjective «atypical» seems misleading as if there were such a thing as «typical» proliferation. Of course the word «borderline» lacks the concreteness, and is rather general, but still it reflects the major feature of S-BOTs - the intermediate character of their clinical course. Kurman [6] was against the use of any connotations of malignancy including "limited" because he considered that the cells of S-BOTs lacked marked destructive capacities. In his view the majority of S-BOTs are benign and patients do not die from the disease, but do die from complications, such as adhesions for example. This opinion seems to be rather one-sided. Malignancy is a complex clinicomorphological and not isolated microscopic notion. Many malignant tumors do not give widespread metastases, or destroy surrounding structures, but cause death by compressing vitally important foci (e.g. brain tumors). Even serous carcinoma, one of the most grave and incurable cancers, often does not produce metastases in the parenchyma of the organs (lung, liver). It only gives massive overgrowth not penetrating deeply into organs and causes death through mechanical obstruction and intoxication due to the intensive processes of cell death. Moreover there are more and more cases where patients with S-BOTs develop late, sometimes fatal, relapses. And finally, as correctly stated by the authors of the Workshop [5]. «It is possible to argue that the relative survival of women with S-BOTs localized to the ovary approximates that of women without cancer in the general population. This fact alone does not prove that S-BOTs are benign, because many malignant tumors localized to the organ of origin are reliably cured by excision». So until our comprehension of the subtle mechanisms of cellular growth of S-BOTs is clarified, the term «borderline» should be preferred to «atypical proliferative» temporarily in spite of its arbitrary nature.

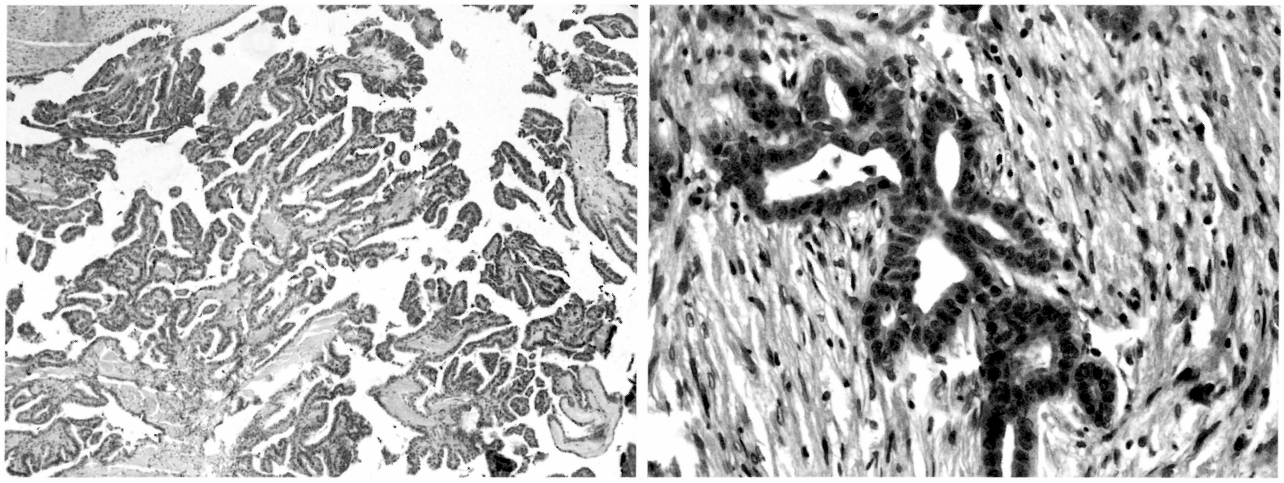
According to the definitions of the WHO classification [8], S-BOTs are tumors of cystic-papillary structures. The papillae are covered with two types of cells: tubal and mesothelial. S-BOTs have the clear-cut tendency for bilaterality and coexist with extra-ovarian dissemination. The genesis of the latter is obscure. S-BOTs develop late recurrences with the formation in the pelvis and abdomen of nodules and cysts in some cases adherent to the urinary tract. Some of the patients die from further progression of the disease.

Historically, according to the first WHO classification [9], the structure of the primary ovarian tumor was considered as a prognostic guideline and the peritoneal implants as factors not influencing prognosis. However soon thereat clinical practice forced us to radically change this attitude and pay greater attention to the microscopic characteristics of the implants. Different classifications of the implants were introduced dividing them into invasive and noninvasive types [10]. The implementation of these types in diagnostic practice met with serious difficulties. The anatomical structure of the omentum and serous coverings of the peritoneum do not permit objective and proper classification of the implants [11].

Meanwhile pathologists once more returned to the assessment of the primary tumor trying to discover some new markers of malignancy. Briefly, the main topics of discussion in the literature are a further subdivision of S-BOTs, with the introduction of a new variety - micropapillary S-BOT, plus the role of exophytes in the dissemination of the S-BOTs, microinvasion, implants, lymph node involvement, etc. [3, 4].

Many authors believe that the frequency of implants is significantly dependent on the macroscopical features of the tumor, the presence of exophytic growth on the surface of the ovary [12]. Indeed, it is logical to suppose that dissemination of the tumor cells occurs easily from the exophytic papillary structure of the primary tumor. Our experience does not confirm this supposition. In a group of 60 cases of S- BOTs out of 31 cases with exophytic excrescences on the surface 28 patients had implants, but of the remaining 29 patients without an exophytic component 18 patients also developed peritoneal implantation. The frequency of extraovarian spread in cases with exophytic surface growth is definitely higher but 18 patients with implants in the intracystic group of cases are not insignificant either. Besides, for the proper assessment of the relationship between the primary tumor and implants not only is their coexistence important but also their structural identity. A priori one can assume that if the implants were the results of simple detachment of the cells from the papillae of the primary tumor there should be a microscopical similarity between them, if not complete, may it still reproduce some principal features of the primary. Is this so? In fact, a comparison of the microscopic features of the tumors represented by exophytic growth with those of implants shows that very often the latter significantly differ from the former with regard to their cytological properties. In the implants of the above-mentioned patients, the cells may be much more polymorphous, sometimes even anaplastic, mixed with many psammomatous bodies, often building minute papillary or tubular structures (Figure 1 a, b). It is worth noting that the fact of cytological differences in the sense of a more anaplastic character of the implant constituent cells is not induced by preceding chemotherapy and may be documented in untreated patients as well. The same discordance between the primary tumor and implants has been noted in cases with intracystic S-BOTs.

Assessing the microscopical structure of the primary tumor the pathologist first of all pays attention to the cellular polymorphism of the neoplasm. The major factor in tumor behavior traditionally is considered cellular atypia. S-BOTs do not belong to the neoplasms with marked cellular atypia, but we could still discern the tumors with normal N/C (nuclear/cytoplasmic) ratio cell constituents and the overtly enlarged cells with a high N/C ratio. Some of the last cell types are encountered in patients with preoperative chemotherapy, including intraabdominal. Cellular polymorphism



g. 1a Fig. 1b

Figure 1. — Different microscopic patterns in the primary S-BOT and implants.
a) Exophytic papillary S-BOT of the ovary (H&E x 50).
b) Omental implants of the same tumor represented by confluent tubules (H&E x 120).

to some extent could be assigned to therapeutical pathomorphosis, but in untreated patients who developed implants, atypia was encountered in only half of the cases. Even if we exclude treated cases we find that the cellular atypia in the primary tumor does not influence prognosis and is not connected with a definite type of implant.

Much attention has been drawn to the recently separated entity, or subtype of the S-BOTs - micropapillary S-BOT [13]. The Workshop established the micropapillary/cribriform type of S-BOT. "These tumors are characterized by elongated filiform 'micropapillae' that arise directly in a nonhierarchical fashion from cyst walls or form large fibrous or edematous papillae...". Tumors in which cribriform nests of epithelium line papillae are also included in the micropapillary group" [4]. The separation of this subtype evidently has some grounds and the suspicion of its prognostically unfavorable character is well explained since the form of micropapillary growth indicates that epithelial cell proliferation occurs at a much faster rate than that of stromal cells which is always alarming. The same discordance over the stromo-epithelial relationship is reflected in micro-cribrous structures, which are in fact sometimes encountered in S-BOTs. We have seen cribrous structures separately from micropapillary ones, in the fibrous stroma of the primary S-BOTs.

According to the literature and in our own experience these above-mentioned structures are often associated with implants, but their impact on the outcome of patients seems insignificant if it exists at all. We have documented some ten patients with expanded micropapillary patterns who have lived 15 years and more without relapses. The cases with many cribrous structures were often associated with implants, but the survival rate of the patients was excellent - 22, 22, 24 years. Only one patient developed metastasis to the lymph node of the supraclavicular region.

Since the early 70's pathologists have searched for any signs of stromal destruction in S-BOTs and special attention has been drawn to the foci of microinvasion [14, 15]. The Workshop classified them into two groups: eosinophilic cell pattern and «other» patterns. In the eosinophilic cell pattern, one can demonstrate "individual cells or clusters or nests of cells with abundant eosinophilic cytoplasm in the stroma of the tumor ... Tissue spaces or clefts around tumor cells which may simulate lymphatic spaces are often present" [4]. The *others* show "stromal infiltration by small solid nests of cells, branching papillae, elongated micropapillae, or cribroid masses of epithelium" [4]. Indeed several microinvasive patterns may be encountered in S-BOTs. In addition to the mentioned microinvasive patterns we have noted small sized glands in the angiomatoid stroma, minute papillae in the blood vessels beyond the tumor nodule, etc.

We tried to establish a connection between microinvasion and the presence of implantation. In our experience among the cases with omental or peritoneal implants there were both types of patients: those whose primary tumor showed persuasive signs of invasion and those whose primary tumor did not contain detectable foci of microinvasion. Three major possible explanations may exist: 1) either we are not yet able to detect all minute microinvasions; or 2) these foci are extremely small; and 3) there is no causal relationship between microinvasion and the extraovarian spread of the tumor.

I should mention something from my personal experience which is not based on statistically significant figures but merits interest. Those patients whose primary tumor did not show foci of microinvasion had mainly noninvasive types of implants, represented by differentiated glands lined with mature cells indistinguishable from those of surrounding endosalpingiosis.

The most intensive discussions have arisen about the types of implants in S-BOTs. As we have already mentioned the pendulum of interest in this phenomenon has swung from total denial of their significance to overt overestimation

of their importance as a prognostic factor. The difficulties in dividing them into two groups – invasive and noninvasive – methodically are insoluble. In fact the sites of dissemination – adipose tissue of the omentum and the mesothelial covering of the peritoneum, contain few, if any points of reference to properly confirm invasion. Even theoretically, why is the implant noninvasive if it grows in the tissue of the omentum superficially beneath the serosal covering and shows no transition to the foci of endosalpingiosis? Some implants may grow deeper while others remain in the upper portion of the omentum. In the Workshop formulations, desmoplastic implants are regarded as noninvasive if there is a sharp interface between the tumor-fibrous tissue and the underlying normal tissue [4]. Theoretically, from the point of view of classic oncomorphology, the criterion is rather questionable. Parameters, such as the massive voluminous character of the implants, large solid nests, necrosis, destruction of the tumor cells and the surrounding tissues seem to us to be much more reliable. Also very important are in our opinion the presence of cellular polymorphism and signs of anaplasia in the implants,a phenomenon already noted by other authors [10]. The analysis of our material revealed that many patients with typical S-BOTs, which were sampled thoroughly, and had noninvasive nondolent implants defined according to the Workshop criteria died in three to five years with signs of dissemination of the disease, with metastasis in the lung and lymph nodes. At the same time patients with also typical primary tumors and so-called invasive implants survived ten years or more, even up to 30 years free of disease. Most probably, it will be necessary to search for new criteria to determine the real importance of the structure of the implants in the natural history of the disease.

As for assessing the character of the implants and their relationship with the primary ovarian tumor, there is another point of view, which merits greater interest. The idea is that extraovarian implants are the substrate of another disease, which proceeds in parallel with S-BOTs, e.g. that of serous carcinoma of the peritoneum [1]. The assumption seems logical in the context of the existence of primary serous borderline tumors of the peritoneum as well [16]. The Workshop gives another theoretically clear-cut formulation [5] according to which there may be three pathways for the development of invasive implants in women with S-BOTs. "Pathway 1: The borderline tumor undergoes malignant changes in the ovary and spreads via a metastatic process. Pathway 2: Benign tumor cells arrive at an extra-ovarian site via a passive process such as mechanical detachment or transport via the lymphatics; malignant change occurs after the benign cells have implanted. Pathway 3: Implants develop concurrently or metachronously from nonovarian epithelium and are not clonally related to the BOT". Personally, I am inclined to support the idea of a different mechanism of dissemination of S-BOTs. In many cases when patients with S-BOTs died shortly after establishing diagnosis, the cytological patterns of the implants did not coincide with those of the cells of the primary tumor. They were more anaplastic than those of the primary. In such cases we have to assume that either these are really two combined separate pathological entities, or during progression of the disease the cells with higher invasive properties in the primary are selected and then they, and only they, disseminate. The final solution of the problem is possible only after applying elaborated methods of clonal analysis to S-BOTs and their implants [17, 18].

The assumption that S-BOTs are compound processes with multicentric and multistep genesis is to some extent proved by analysis of the microscopic structures of their late relapses.

We have had the opportunity to follow-up the relapses of S-BOTs for almost a 50-year period. These relapses developed on a disease-free background after 20-30-50 years. All patients had typical S-BOTs without marked cellular polymorphism or a micropapillary component (Figure 2a). The single clinical symptoms were those of urinary tract obstruction, since in the majority of the cases the recurrent tumors were located in the pelvis and often adhered to the ureter. Macroscopically they were predominantly cysts filled with a transparent liquid, sometimes multilocular with papillary growth on the inner surface of cystic walls (Figure 2b). Sometimes we encountered small microscopic tumors in the adipose tissue and muscles of the pelvis (Figure 2c). Detailed analysis of the microscopic structure of these small cysts revealed continuous transitions from the highly differentiated epithelial structures to the mesothelial lining of the pelvic peritoneum (Figure 2d). All these support the assumption that late relapses of S-BOTs are the reflection of the multicentric genesis of the disease and by no means indicate the terminal stage of the disease. If the surgeon manages to decompress the urinary tract, the patients live ten or more years after these operations with no decrease in the quality of life. It should be stressed that the number of late relapses increases as time passes and the more patients are reinvestigated after many years of an indolent course of the disease.

Some words on the lymph node metastasis of S-BOTs. It rarely occurs, but is very confusing. In two cases we encountered retroperitoneal lymph node metastasis two years after initial treatment. The cellular composition of the cases resembled that of mesothelial-type cell agglomeration. Only three to four years have passed, so we cannot assess the possible negative impact on the outcome of the disease. In some cases the lymph nodes were not removed though fine needle aspiration was performed. As far as one can rely on the cytological description, the cells in the metastatic foci lacked any marked signs of anaplasia. Much more histologically proven cases of metastatic S-BOTs have to be studied to elucidate the importance of lymph node involvement in described cases.

I would like to discuss separately seven cases, which are examples of a fatal course of S-BOTs after systemic chemotherapy, but of unknown mechanism. All these patients manifested the disease with ascites and in some cases with pleuritis. Ascitic cells were cytologically diagnosed as high-grade carcinomas (all cases belonged to the early 60's). The patients received short courses of chemotherapy and were operated on within 20-25 days. A thorough study

g. 2a

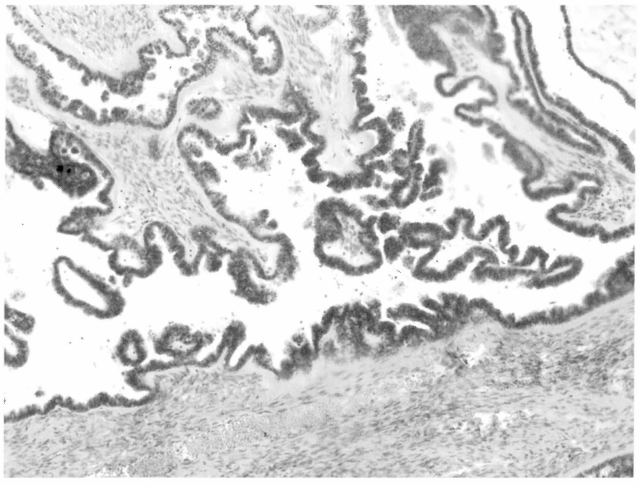
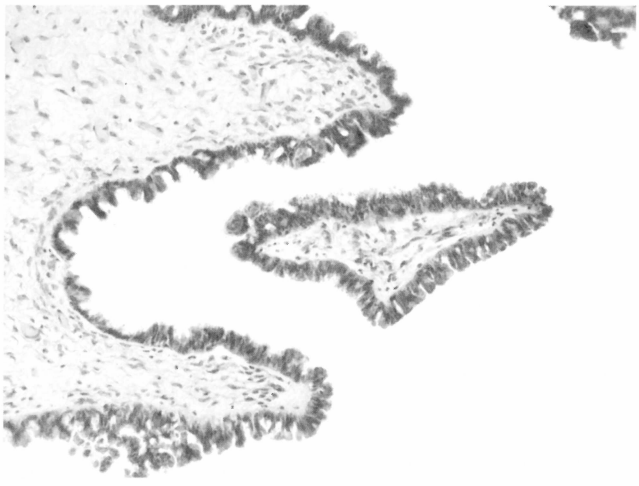


Fig. 2b



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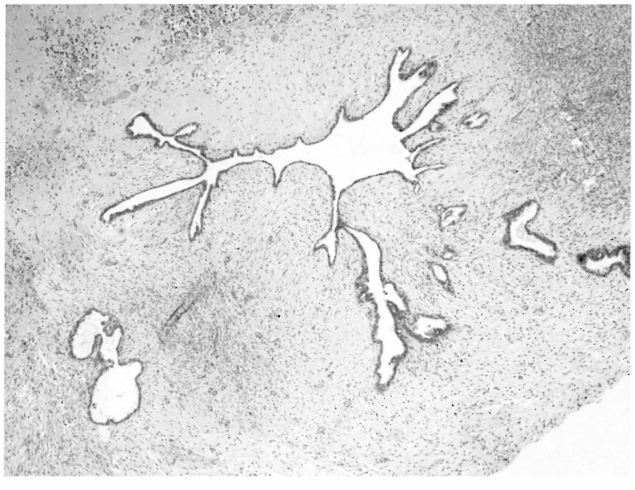


Fig. 2d

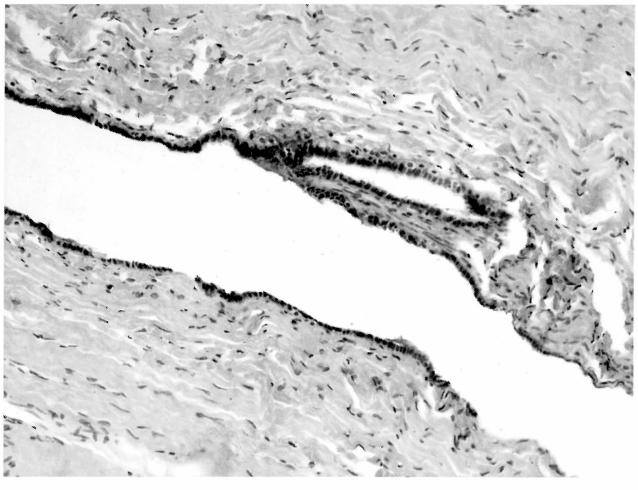
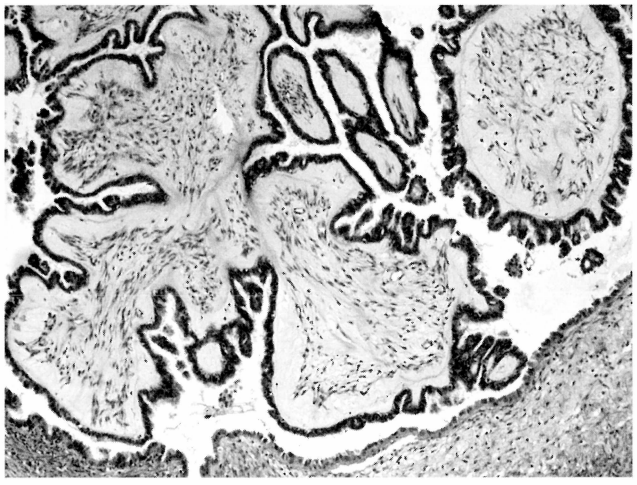


Figure 2. — Microscopic structure of late relapse of a S-BOT.
a) Primary ovarian tumor (H&E x 50).
b) Lining of the cyst in the pelvis (H&E x 100).
c) Small cysts in the pelvic muscles (H&E x 30).
d) Transition from the peritoneal lining to the small invaginating gland in the wall of a small cyst (H&E x 100).

of the postoperative specimens showed uniform S-BOTs without any marked proliferation (Figure 3a) and with the noninvasive implants (if we use today's nomenclature) - mesothelial type papillae with a single layered covering (Figure 3b). The patients soon showed signs of progression, and two of them were repeatedly operated on for bowel obstruction. The tumoral nodes removed at these urgent operations also lacked signs of destructive growth, anaplasia. In spite of intensive chemotherapy the patients died with intraperitoneal dissemination and pleuritis, with suspicion of lung metastasis over three to four years. For a long time the cases were considered as carcinomas in which the absence of anaplastic structures were ascribed to the cancer cell eliminatory effect of the chemotherapy. At first glance it seemed to be so, but more detailed analysis of the cases cast some doubt on such an interpretation. Of course, chemotherapy could cause cancer cell death and disappearance, but as a rule in such cases some residual dystrophic cells survive, or one sees the remnants of necrotized structures. Moreover, chemotherapy cannot entirely reconstruct and remodel the structure of the tumor. The most plausible explanation is that these tumors contained small foci of aggressive clones or undifferentiated cell masses of stem cell type, which were responsible for disease progression. Such hidden clones may exist in many S-BOTs and remain undetected by contemporary methods. Furthermore, chemotherapy may even favor their progression rather than supress them. From this point of view it is clear why the opinion on the accelerating effect of chemotherapy on the course of S-BOTs exists [11]. We refer to systemic chemotherapy since in our experience local intraabdominal chemotherapy, especially together with hyperbaric oxygen therapy, or administration of polymer-associated chemotherapeutical agents induced long remission in many cases. The same can be said about the intraabdominal administration of radioactive isotopes. Nonetheless, the role of chemotherapy in S-BOTs (especially of platinum compounds [19]) must be reconsidered and new schemes and drugs should be administered in systematic and cooperative studies.

Fig. 3a



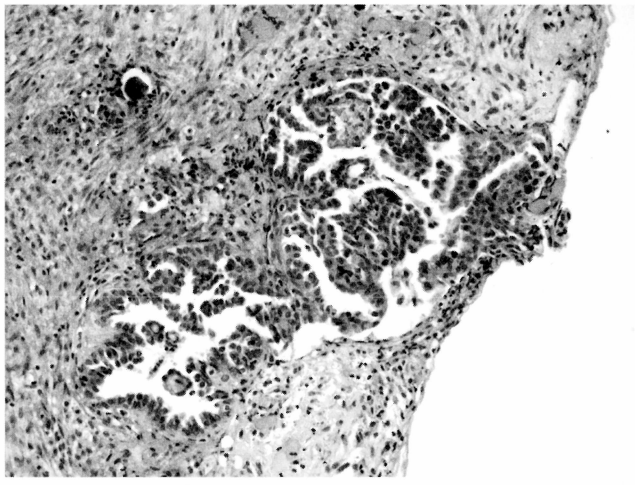


Fig. 3l

Figure 3. — S-BOT with fatal course treated with chemotherapy.
a) Primary ovarian tumor (H&E x 50).
b) Noninvasive omental implants of the same patient (H&E x 50).
Both photos after several courses of chemotherapy.

How can we summarize the up-to-date situation of S-BOTs? What do we know of certainty? We can affirm that S-BOTs are a group of cystic-papillary tumors with a serous-mesothelial covering and marked tendency for bilateral growth. The cells of moderate atypism are their main constituents; the signs of microinvasion and even the foci resembling highly differentiated serous carcinoma are encountered. S-BOTs very often coexist with an extraovarian intraabdominal component. The latter is represented by a broad spectrum of structures from endosalpingiosis to serous cancer. Sometimes these structures are connected with each other via transitions, and in other cases simply coexist. Part of these implants do not induce any cellular response while in a good deal of cases an angiomatoid or desmoplastic reaction, or calcification occurs.

In several cases the patients with S-BOTs develop distant metastases, in 6-7% - late relapses. The latter most probably are of local origin from the mesothelial covering of the peritoneal cavity. Death is due to respiratory insufficiency (distant metastases) or obstruction of the urinary tract (local, mainly late relapses). The role of chemotherapy is unclear, in some cases it may be of benefit, while it can induce progression in others.

Is it possible at present, without knowledge of the molecular mechanisms of cancer growth, to give a rational explanation of the above-mentioned facts? Evidently not. On the other hand can we adopt certain algorithms, which although of temporary character may serve as a guideline for clinicians to manage the patients? Probably yes. In our opinion the clinicians of today may accept the following assumption: S-BOTs are particular cases of simultaneous neoplastic transformation of the peritoneal mesothelium and the covering cells of the ovary comprising dynamically changing clonal structures both in the gonad (up to microinvasive carcinoma) and extra-ovarially. The extragonadal component of the disease may also include the cells of a broad spectrum of maturity and malignancy.

In spite of the presence of microinvasion in the primary tumor, clinicians should expect two types of complications 1) dissemination, including distant, and 2) delayed relapses, which can occur up to 50 years later. It is mandatory that physicians warn patients about such a long period of possible recurrence since in practice one generation of physicians cannot cover this period and clinicians should actively search for such complications, establishing contacts with urologists to detect any possible obstruction of the urinary tract at the early stages. As far as chemotherapy is concerned it is advisable to use more broadly local intraabdominal methods of drug administration, including isotopes. Systemic chemotherapy especially with modern compounds should be used with caution, and only in carefully chosen cases. How to choose the cases? Taking into consideration the microscopic structure of the disease at the given specific stage. In practice the point of issue for the clinician is the initial microscopic diagnosis of the S-BOT. Later he seldom controls the possible alteration in the morphological substrate of the disease. The clinician should perform by all possible ways biopsies, using broadly laparoscopic methods of diagnosis at different stages of the disease and change the treatment schedules (if necessary) in accordance with the results of microscopic investigation at a given stage of disease.

The alternative - forecasting the natural history of the patients based on the results of the primary histological investigation seems unproductive at the current stage of our knowledge and requires further progress in oncology. Meanwhile we have to unify our clinico-pathological data in a well systematized, precisely shaped protocoled research including the possibly broad team of participants and collect the cases with a long follow-up period.

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