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REVIEW ARTICLE

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Serous tumors of low malignant potential of the ovary

1. Diagnostic pathology

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Abstract Serous ovarian tumors of low malignant potential (SLMP) – also called borderline tumors of the ovary – represent a heterogeneous group of ovarian epithelial neoplasms. In general, this tumor type has a favorable prognosis. Nevertheless, 10–20% of SLMP exhibit a progressively worsening clinical course, with widespread peritoneal implants and death of the patient within 5 years. The criteria for recognizing the SLMP with an unfavorable prognosis and for distinguishing SLMP from highly differentiated ovarian carcinomas are summarized in this report. The importance of supporting methods, e.g., DNA cytophotometry, is demonstrated, revealing that in most cases aneuploidy can be regarded as an indicator for aggressiveness of the tumor and for poor clinical outcome. The importance of the new concept of micropapillary serous carcinomas (MPSC), the relationship of this variant of SLMP to invasive serous carcinomas, and the prognostic importance of invasive vs noninvasive peritoneal implants are discussed. (The concepts of molecular pathology of SLMP will be discussed in part 2 of this serial paper.)

Key words Borderline tumors · Tumors of low malignant potential · Ovary · Serous tumors · DNA cytometry

Introduction

More than half a century has passed since the initial description of borderline tumors of the ovary [72], yet there is still a lot of controversy about the biology of this specific type of tumor. The following questions are currently matters of discussion: (1) Are these tumors placed correctly between adenomas and carcinomas? (2) How can we explain the presence of peritoneal implants in the absence of an invasive process? and (3) Are there morphological features indicating an invasive capacity? Since these basic questions still have not been completely answered, the terminology currently used is very inconsistent.

The term ‘borderline’ is used in the new WHO classification [60]. It places these lesions between clearly benign and obviously malignant tumors because they exhibit some (Table 1), but not all, morphological features of malignancy. Arguments favoring this hypothesis are the percentage of borderline tumors that are bilateral, ranging between 26% and 50%, which is higher than for adenomas but lower than for carcinomas [67], and the age of the patients, which is also intermediate between adenoma and carcinoma patients’ ages. This fits in well with a so-called adenoma–carcinoma sequence in which borderline tumors are regarded as transition forms between the two ends of the spectrum. Moreover, the observation of morphological changes resembling serous borderline tumors in ovaries prophylactically removed from high-risk women with at least one first-degree relative and one second-degree relative with breast and/or ovarian cancer [58] suggests that there are common pathways in the pathogenesis of both serous borderline tumors and frankly invasive serous carcinomas. Although this concept may be sufficient for the pathologist, it cer-

Table 1 Histological criteria of SLMP tumors

- Epithelial multi-layering of more than four cell layers
- Not more than four mitoses per 10 high-power fields
- Mild nuclear atypia (slight pleomorphism, sometimes prominent nucleoli)
- Increased nuclear/cytoplasmic ratio
- Slight to complex branching or bridging of epithelial papillae and pseudopapillae
- Epithelial budding and cell detachment into the lumen
- No destructive stromal invasion (see Table 2)

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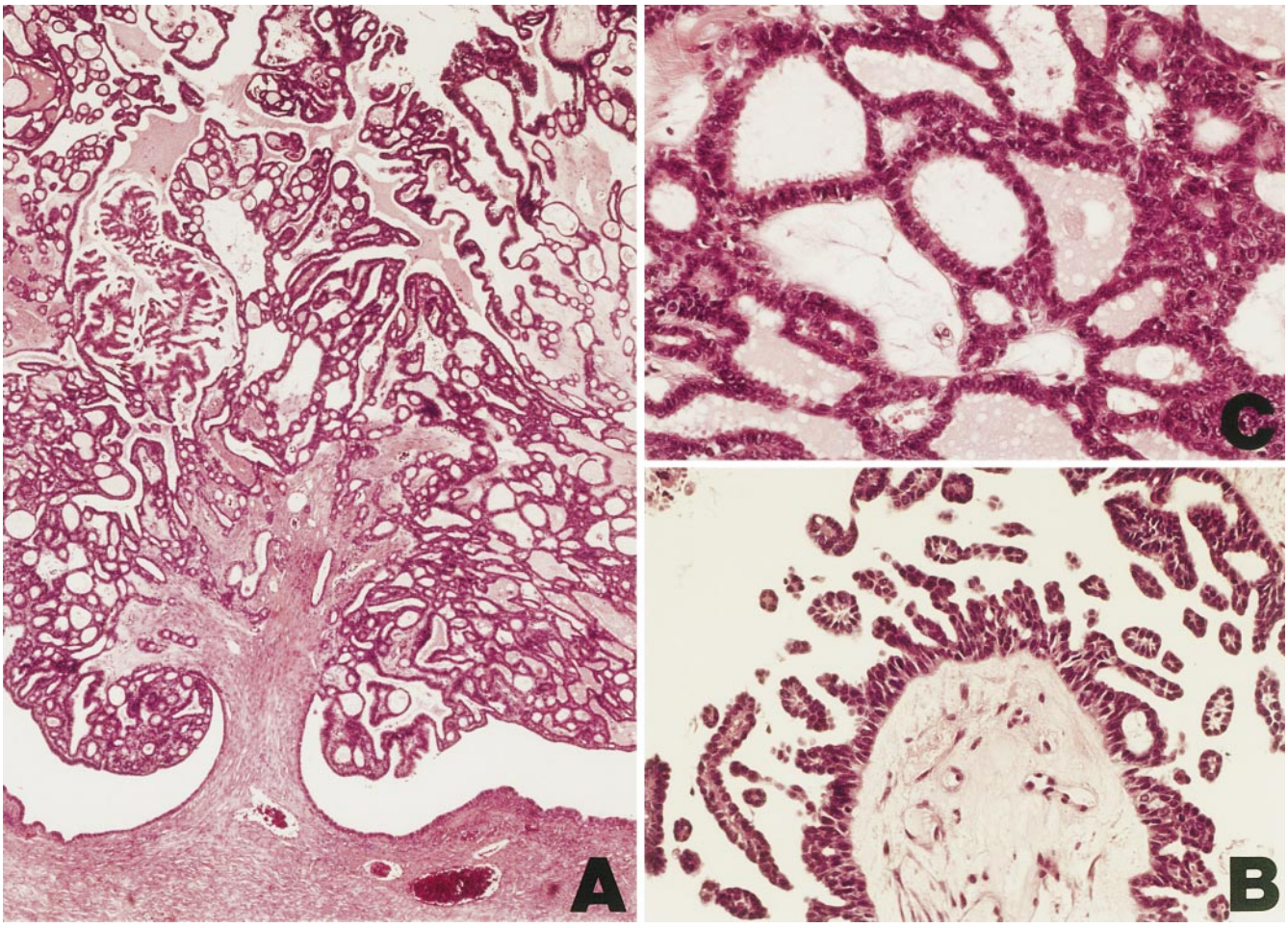

Fig. 1 **A** Typical hierarchical branching of a SLMP with **B** pseudopapillary or **C** cribriform epithelial proliferation

tainly is not for clinicians, because there is no 'borderline therapy.'

Some authors have suggested that these lesions are carcinomas from the beginning. For this reason, Kottmeier et al. [36] introduced the term 'carcinoma of low malignant potential' (LMP). Using this designation these tumors were classified separately for the first time in 1964 in the UICC classification of gynecological tumors [59], and in 1971 by the FIGO [25], the classification then being adapted in 1973 by the WHO [65]. However, it is known that most serous LMP (SLMP) have an indolent clinical course with a 5-year survival rate of up to 99% of the patients with stage I tumors [2, 18,21, 31, 32, 37, 75, 79]. Even if the lesions are distributed throughout the abdominal cavity, i.e. stage III, the 5-year survival rate ranges between 55%–75% [32, 37, 47, 75], and the 10-year survival rate is not significantly worse. This is in sharp contrast to the data available on invasive serous carcinoma of the ovary, which is an incurable disease in stage III with a 5-year survival rate between 15% and 30% [44, 50, 80]. Moreover, the fact that in SLMP often no signs of dedifferentiation occur for many years even if peritoneal lesions persist [9, 23, 29, 33, 34, 69] together with the possibility of regression of stage III SLMP after an oophorectomy [74] initially led to the suggestion that SLMP might be regarded as a reactive-metaplastic process ('müllerian' metaplasia of mesothelial cells). The term 'hyperplastic variety,' used by Taylor [74] to describe what is currently designated as SLMP, anticipates such a mechanism [17, 34, 70, 73]. The fact that SLMP generally arise in women of reproductive age also suggests a hormonal dependence. Since most of these tumors behave in a benign fashion, the LMP concept has been a matter of controversial discussion.

To avoid the designation 'malignant,' the term 'atypically proliferating' has been suggested [66], since recurrences of stage I SLMP are exceedingly rare and the possibility exists that recurrent tumors might represent independent peritoneal neoplasms. However, since in the rare cases with recurrence the prognosis is usually poor, both Silva et al. [66] and Scully [60] recommend retaining the term LMP, giving appropriate advice to the surgeon for obtaining peritoneal biopsies and ensuring follow-up. Because we also subscribe to this point of view, we use the designation SLMP.

An additional point under discussion is whether stage III SLMP indicates a metastatic spread despite the lack of detectable invasion within the primary tumor or rather originates from a multifocal in situ proliferation throughout

the peritoneum. Clonality studies performed on invasive serous carcinomas revealed monoclonality with respect to the X-chromosomal methylation pattern and to LOH analyses [1, 77], whereas those performed on SLMP indicated polyclonality in some cases [38, 41, 43, 56]. A so-called field defect of the mesothelium or instability of the müllerian epithelium has also been suggested as the basic abnormality leading to multifocal tumor development [41]. It is, therefore, highly questionable whether SLMP have a true metastatic potential, as suggested earlier [67].

Histopathology of SLMP

To diagnose SLMP, at least two of the criteria listed in Table 1 are necessary. Moreover, the absence of destructive stromal invasion (for definition see below) is required. Focal or widespread epithelial proliferation of more than four cell layers (with or without papillary projections) is the most obvious histological feature of SLMP (Figs. 1, 2). Epithelial proliferations or atypia of minor degree should be placed into the benign category according to the WHO classification [60]. The appearance of small groups of epithelial cells detached from the epithelial lining (Figs. 1B, 2C) is a clue to the distinction from serous adenomas, which do not show any cell detachment. Proliferation indices have been studied by MIB1 immunostaining. The data show higher epithelial proliferation in SLMP than in serous cystadenomas, whereas proliferation rates of SLMP are below those detected in serous carcinomas. Measures range from 0.1% to 3.3% in serous cystadenoma, 1.3% to 19% in SLMP, and 6.5% to 31% in serous carcinoma [15, 16, 17]. Although the reported mean value for SLMP is below 10%, and thus lower than that for invasive serous carcinomas, there may be considerable overlap with the proliferation indices of carcinomas, and it cannot therefore be taken as a distinguishing feature.

On the other hand, there has been some discussion about whether tumors with high-grade nuclear atypia should be excluded from the SLMP category. In our view this is not justified. However, in the presence of high-grade atypia extensive sampling should be performed, because under careful examination microinvasion or invasion can be found in many cases. In the authors' experience cellular and nuclear features alone are of little value in differentiating between SLMP and highly differentiated invasive serous carcinomas; that is to say that SLMP can show a relatively high degree of atypia (Fig. 2) while well-differentiated serous invasive carcinomas may consist of tumor cells with only mild alterations. This observation has been confirmed morphometrically [35]. Invasive carcinoma should also be suspected if atypical mitotic figures, which are usually not present within a SLMP, are found. An inflammatory or a desmoplastic stromal response is commonly not present in SLMP (see part 2 of this serial paper).

For a clear-cut distinction between SLMP and invasive carcinomas, the histological evidence of stromal invasion is of the utmost importance. This, however, is often difficult to determine, particularly in multicystic lesions with multiple small epithelial inclusions and the often extensively developed orderly penetration of tubular epithelial formations into the stroma. Moreover, different terms have been used to designate various degrees

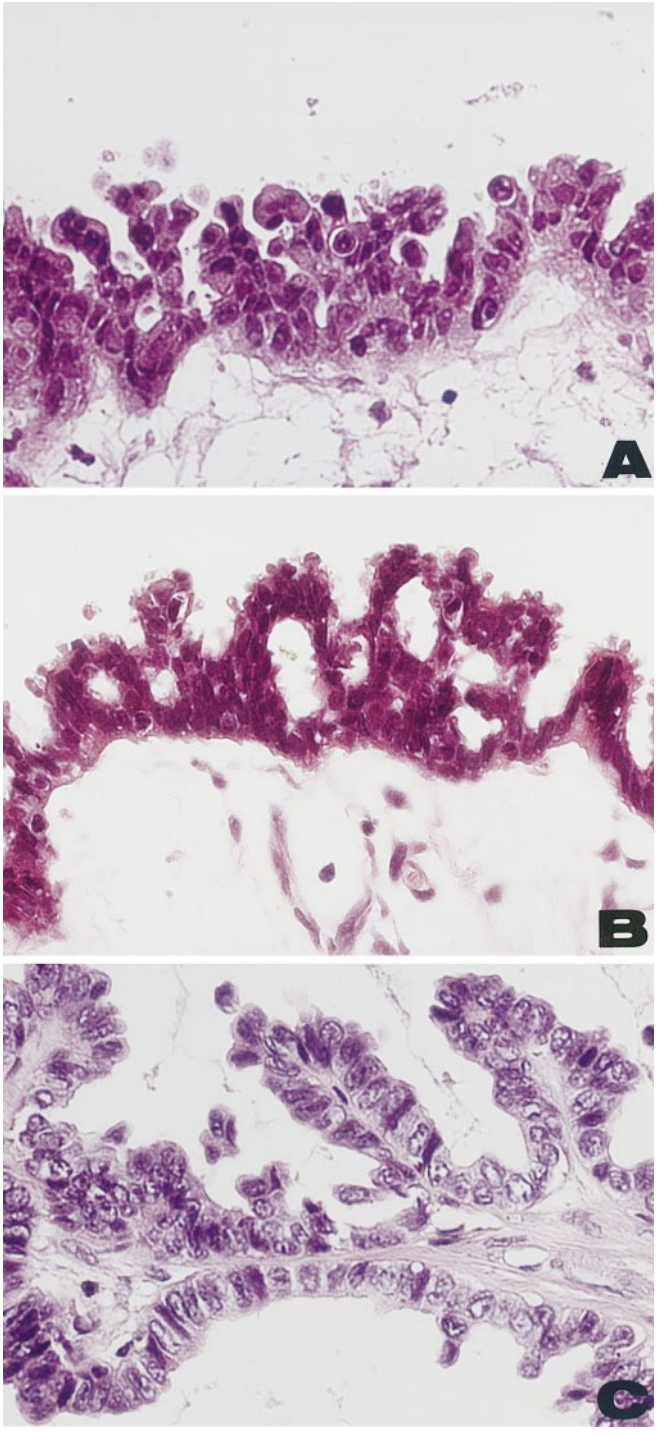

Fig. 2A–C Cytological aspects of SLMP. **A** Low grade atypia with hyperchromatic nuclei and high n/c-ratio (A) or ciliated cells (B) are typically. Moderate atypia with enlarged nuclei and coarse chromatin (C) are less frequently seen

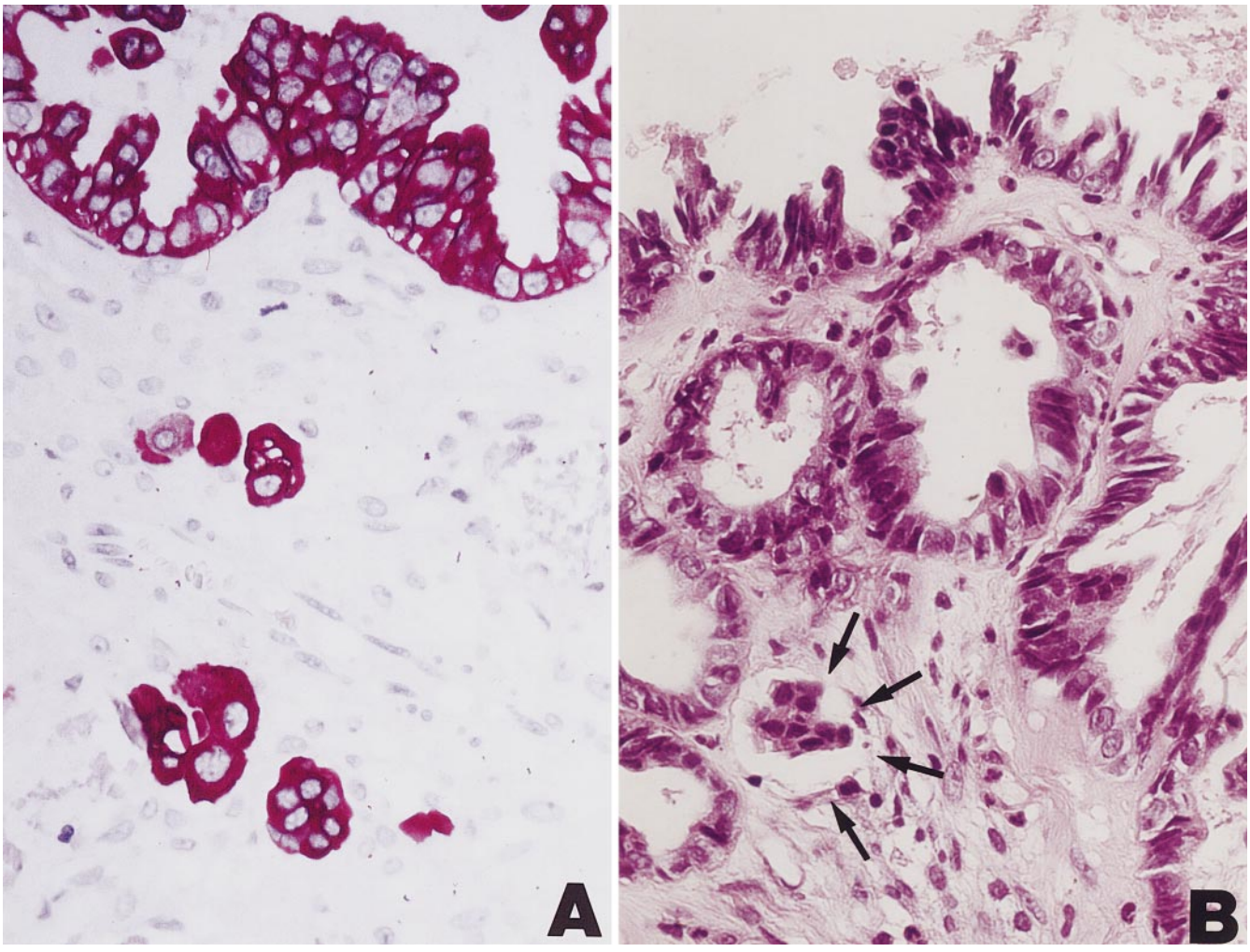

Fig. 3A, B Cytokeratin immunohistochemistry of the microinvasive variant of SLMP characterized by single tumor cells and a small group of tumor cells in the stroma, clearly separated from the overlying SLMP epithelium. As a rule **A** a stromal reaction is lacking and **B** there is invasion of lymphatic spaces (*arrow*)

of invasion, creating some confusion on the diagnostic criteria. The WHO classification [60] recommends the term 'tantamount to invasion' as a supplement to SLMP without stromal reaction where a 'confluence or very close approximation of glands or cysts lined by cells with a high degree of nuclear atypicality' is present.

The term 'microinvasion,' which has been accepted in the new WHO classification [60], is used for invasive foci smaller than 10 mm^2 and less than 3 mm in their longest linear dimension (Fig. 3). Microinvasive foci are composed of single epithelial cells or small solid or cribriform cell groups lying within the stroma or surrounded by an empty space, resembling a lymphatic vessel. Frequently there is no stromal reaction [4, 61, 66, 71]. Microinvasion may include invasion of vascular spaces (Fig. 3B) without substantiating the diagnosis of invasive carcinoma. Approximately 10% of SLMP with microinvasion show this feature. There is probably no prognostic significance of microinvasion, although too few cases have been reported for a definitive conclusion to be possible [4, 32, 71]. It is, however, remarkable that an association obviously exists between microinvasion and stage of the disease [66]. Moreover, it is interesting to note that in one study nearly one-third of patients with microinvasive SLMP were pregnant [4].

Invasive carcinomas are characterized by the presence of so-called destructive stromal invasion (Table 2). To reduce the risk of overlooking invasion it has been suggested that at least one tissue block be taken per centimeter of the lesion.

Table 2 Destructive stromal invasion

- Tentacular (and not broad), finger-like epithelial projections into the stromal interface
- Haphazardly arranged neoplastic glands, small cell groups or single cells with higher degree of cytological atypia than in the noninvasive part of the tumor
- Stromal changes from hypercellular, fibrous or hyalinized to reactive immature (desmoplastic) with thin-walled sinusoid vessels and an inflammatory infiltrate
- Absence of basement membrane around invasive elements
- The area of invasion should exceed 10 mm^2 in area or 3 mm in its longest dimension (see microinvasive variant of SLMP)

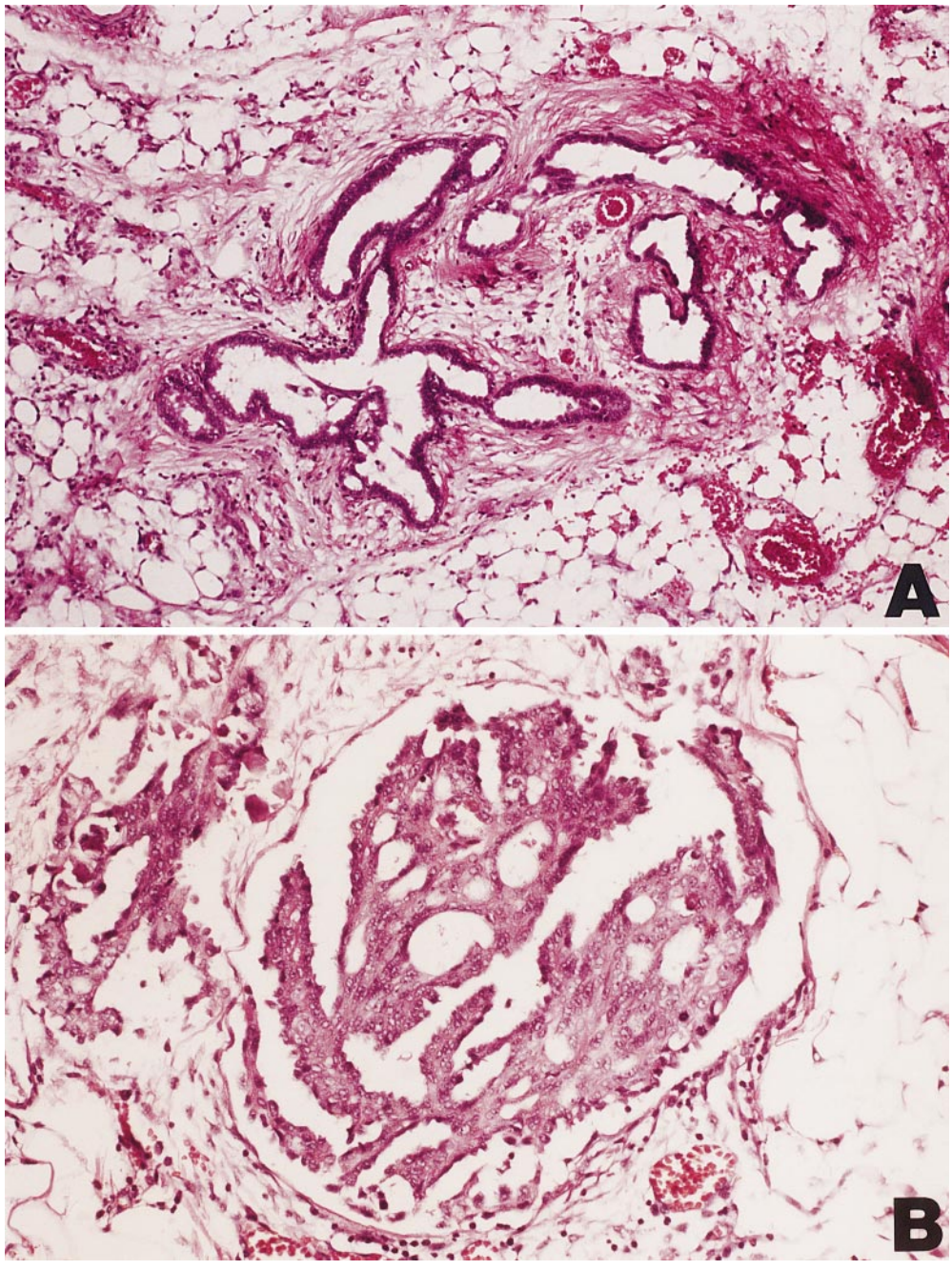

Fig. 4 **A** Noninvasive desmoplastic peritoneal implant composed of tubular epithelial proliferation surrounded by connective tissue containing inflammatory cells. **B** Invasive implants are characterized by papillary or pseudopapillary epithelial clusters surrounded by a clear space

Prognostic importance of ovarian surface proliferations, peritoneal implants and lymph-node involvement

Approximately 25% of SLMP are associated with tumor cell proliferation on the outer surface of the lesion without evidence of tumor cell permeation from the inner surface of the cystic tumor. More than 90% of SLMP with surface proliferations (SP) develop peritoneal implants (PI) [62], and only 4% of patients with PI had no SP.

Even though the occurrence of SP is not strikingly correlated with a poorer clinical outcome, PI should be carefully evaluated, since two prognostically different types of PI have been characterized: 'noninvasive' (for criteria see Table 3; Fig. 4A) and 'invasive' (for criteria see Table 4; Fig. 4B). The former is further subdivided into a desmoplastic and an epithelial type of noninvasive PI. While the noninvasive implants (desmoplastic and epithelial types) have almost no negative influence on the long-term survival with respect to 10-year survival rates, the invasive form is associated with a poor prognosis, i.e. more than 50% of patients develop recurrences and the 10-year survival rate is only 33% [5, 6, 19, 20, 24, 45, 48, 53–55, 57, 63]. Therefore, morphology of the peritoneal implants is probably one of the main prognostic factors in patients with stage III SLMP, although oth-

Table 3 Noninvasive peritoneal implants

Desmoplastic type
• Cell complexes or gland like structures plastered on the surface of the peritoneum or in the submesothelial space
• Dense fibroblastic or granulation tissue-like stromal reaction, merging with the epithelial cells
• Numerous psammoma bodies can be present
Epithelial type
• Exophytic or endophytic proliferations with thick, hierarchical branching papillae
• No stromal reaction
• Frequent psammoma bodies

Table 4 Invasive implants

• Haphazardly distributed glands or micropapillary proliferations invading normal tissue
• Loose or dense fibrous stromal reaction without significant inflammation
• Cell clusters often surrounded by a clear space of artificial origin

er authors have failed to confirm the prognostic importance of invasive PI [34, 46].

Again, the main problem lies in defining criteria for the diagnosis of invasive implants. Those used by Seidman and Kurman [63] are summarized in Table 4. Invasive PI have a dominating epithelial component with highly complex epithelial proliferation, micropapillae and small nests of cells, whereas noninvasive PI have a scant epithelial component composed of irregular islands of neoplastic cells merged almost imperceptibly with the stroma cells or plastered on the peritoneal surface or extending as septa between lobules [60]. Whenever the epithelial component within a desmoplastic PI exceeds one-third of the area, invasion should be suspected [60].

Eichhorn et al. [12] have focused on the morphology of the underlying tissue, which has to be clearly replaced or destroyed for diagnosis of an invasive PI. However, if cells with 'obviously malignant features' are present they allow diagnosis of a carcinoma regardless of other features of the implant. This is justified by the fact that even frankly invasive serous carcinomas may give rise to noninvasive PI [5, 42]. Moreover, it has been suggested that marked nuclear atypia and aneuploidy [48, 51] are of prognostic significance even in the absence of invasion. Therefore, noninvasive implants should be evaluated from the viewpoint of their possible carcinomatous nature.

The term 'microinvasion' has also been used for PI, and in this localization it depends on the number of invasive cells, and not on the size of the focus. When a 'significant amount' of invasive cells are present Silva suggests the diagnosis of an invasive implant, whereas the presence of few invasive cells within a prominent fibrosis is called 'early invasion' or microinvasive implant [66]. Microinvasive implants probably have no influence on the prognosis. Whether the expression of CEA and LeuM1 is helpful in the diagnosis of invasive PI [67] needs further investigations.

Another question is whether there is a real biological difference between the so-called foci of endosalpingiosis [67] occurring in the absence of ovarian lesions and noninvasive PI accompanying a SLMP, and whether peritoneal lesions resembling endosalpingiosis in the presence of a SLMP allow its classification as stage II. Interestingly, the morphology of endosalpingiosis in the presence of SLMP was found to depend on the occurrence of recurrent disease [66]. It has been suggested that a focus of endosalpingiosis might be the precursor of what is called noninvasive PI, probably representing a higher tendency of the mesothelium to undergo müllerian metaplasia or to develop proliferative changes. The biological impact of 'atypical endosalpingiosis' remains unclear. The lack of uniform diagnostic criteria for all these peritoneal lesions makes it difficult to compare the data from different studies.

The genesis of peritoneal implants is a subject of intense discussion. The two opposing hypotheses are implantation and multifocal development. Whereas Kurman's group believes that PI represent metastases from an occult invasive ovarian carcinoma or are implants from SP [66], Russell favors the notion of an independent development of PI [56]. The latter point of view is based on the concept of a secondary müllerian system [77], which includes the peritoneal cavity in an expanded reproductive system. This would also explain the similar range of lesions occurring in the peritoneal cavity in the absence of any ovarian pathology [3]. In this context, peritoneal lesions accompanying SLMP are perceived as neoplasms in their own right or, in other words, invasive PI represents a synchronous extraovarian peritoneal carcinoma. Scully explains the incongruity of noninvasive ovarian lesions forming an invasive PI claim by a higher resistance of the ovarian stroma than of the adipose omental tissue to invasion by tumor cells, or by alterations to the tumor cells when they implant into the peritoneum [66].

Data on the frequency of lymph node involvement in SLMP tumors range from 21% to 50% [11, 26, 40, 78]. This is a surprisingly high rate, but it is seemingly devoid of any prognostic influence. The question is whether these epithelial foci are true lymph node metastases or rather hyperplastic mesothelial cells inside the nodes, as suggested in a recent report about the differential diagnosis of these two lesions [8]. Moreover, some foci seem to arise within lymph nodes from müllerian inclusion glands [27, 28].

SLMP with favorable versus unfavorable prognosis

There are concordant observations published by numerous authors [7, 9, 10, 31, 32, 37, 41, 76] of a subgroup of approximately 10–20% of SLMP which behave like frankly invasive cancer, causing death of the patients without being recognizable in conventional histology.

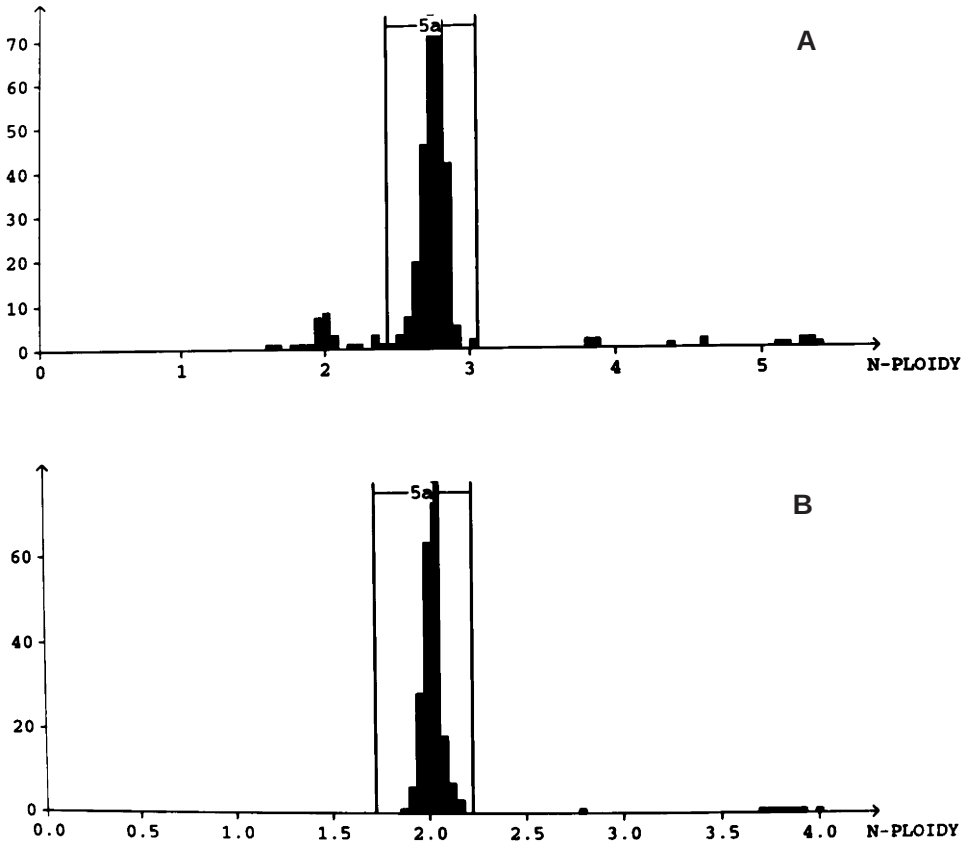

Fig. 5 DNA histogram of **A** a microinvasive SLMP (same tumor as shown in Fig. 3B), with an aneuploid stemline at 2.75c, in contrast to **B** a diploid stemline of another SLMP

Moreover, several studies report that about 30% of SLMP may recur [13, 30, 52], showing up with a worse prognosis as recurrences. The identification of the tumors that bear a risk of recurrence or progression to invasive serous carcinoma is of great importance, because the patients with such tumors are the only ones in whom therapy as for stage I invasive serous carcinoma would be indicated. Many studies have been performed in attempts to differentiate between SLMP with a low risk of progression and those with a higher risk. Although some reports focus on the presence of a high mitotic index and an increased cellular atypia as possible indicators of a higher risk of relapse [5, 13], there are currently only two approaches of significance: DNA cytophotometry and, probably, the 'MPSC concept' (see next section).

Extensive studies applying flow and static DNA cytophotometry have been performed. Most of the results were obtained by flow cytometry, which has the disadvantage that minor genetic alterations are easily overlooked. Thus, for a diagnostic approach to SLMP, static DNA cytometry should be performed on single-cell suspensions from the paraffin-embedded material according to the guidelines of the 1997 ESACP consensus report [21]. The results obtained by DNA cytometry consistently show that up to 95% of SLMP display a diploid DNA histogram, with few cells in the 4c region, indicating their low proliferative activity and only minor genetic alterations [10, 13, 14, 30]. Diploid SLMP are almost always associated with an excellent clinical outcome [30, 51], although Tan et al. [68] found that exceptions do occur. On the other hand, aneuploid LMP tumors – characterized by a stemline deviation (Fig. 5) – have a high recurrence rate, and the patients frequently die of their disease. These are the reasons why, in the case of aneuploidy, we recommend a therapy of the kind administered for a low-grade invasive serous carcinoma. In the experience of the authors, aneuploid SLMP are frequently associated with microinvasion. In addition, DNA cytometry is of prognostic importance in extraovarian lesions, because aneuploidy of PI was found to be the most important prognostic factor [48, 51]. The conclusion derived by Seidman et al. [64] from their findings, that aneuploidy is not related to tumor progression in SLMP, and particularly in stage III tumors, is in contrast to our [10] and other authors' observations [14, 51].

The concept of micropapillary serous carcinoma

In 1996, Burks [6] described a subset of SLMP, compromising 5–12% of cases of this tumor, which fulfilled the criteria as summarized in Table 5 and which he designated 'micropapillary serous carcinoma' (MPSC). Patients with these tumors (in particular those with pure micropapillary structure) are usually younger than those with conventional SLMP, and MPSC seem to be biologically different. Their separation as a distinct subtype is based on the lower 10-year survival rate (68–71%) than in patients with conventional SLMP and on their higher frequency of advanced stage, bilaterality, and ovarian sur-

Table 5 Histological criteria of 'micropapillary serous carcinoma' (MPSC)

- Fine papillary and pseudopapillary structures which are at least five times as long as wide, arising directly from plump papillae with a thick fibrous centrally located stock (nonhierarchical branching creating a „medusa-like" appearance)
- Sometimes focal cribriform growth pattern with surface bridging
- 5 mm continuous growth of this pattern

face involvement (advanced stage: 48–66% vs 32–35%; bilaterality: 59–63% vs 25–30%; SP 50–65% vs 36%). Moreover, with tumors of this type there were more invasive implants and more progressive disease [6, 12, 63]. Probably for these reasons the micropapillary pattern has been taken note of in the new WHO classification, albeit without formation of a separate entity [60].

To summarize the data of Eichhorn et al. [12], there is still no convincing evidence that patients with MPSC stage I or even higher stage lesions accompanied by noninvasive implants have a poorer clinical outcome than patients with conventional SLMP. Moreover, these authors found no evidence that MPSC with invasive implants exhibited a different prognosis than conventional SLMP with invasive implants. Therefore, they suggest avoiding the designation 'carcinoma' because the biology of micropapillary tumors is closer to that of the borderline category than to that of frankly invasive carcinomas, even in the presence of invasive implants. On the other hand, Kurman and his group believe that MPSC represents a fully fledged carcinoma even in the absence of stromal invasion, with a biological potential exceeding that of typical SLMP (e.g. higher frequency of bilaterality, and involvement of the ovarian surface) [66]. Although the presence of 'more florid epithelial proliferations' has already been mentioned by Silva as suggestive of the presence of an invasive process, there are reports of studies that did not find any prognostic value of micropapillary growth in otherwise typical SLMP [29]. Moreover, all patients with MPSC in stage I reported so far have survived, indicating that in the absence of peritoneal implants the micropapillary pattern per se has no prognostic implications. Therefore, it has been suggested by Russell that it is not worth the effort to establish criteria implying invasive capacity in its absence, because the morphology of the peritoneal implant is the critical factor [66]. However, the number of stage I tumors in this category is still small. Therefore, more data on the biological behavior of this morphological variant of SLMP and more reproducible criteria for their diagnosis are needed before its classification as a distinct subtype of SLMP is justified.

Conclusion

The conceptual framework of SLMP is shifting. Nevertheless, a number of questions on the biology and pathogenesis of SLMP and its implants remain open: (1) Is there a progressive multistep carcinogenesis from benign through SLMP and then on to malignant ovarian tumors? (2) Do SLMP with favorable outcome differ from those with unfavorable outcome from the beginning, or are they two variants of the same disease? and (3) Why do so-called noninvasive implants behave in a distinctly different manner from so-called invasive implants? Independently of these and other questions, both the diagnostic criteria and the terminology need to be standardized to obtain comparable data with sufficient follow-up. For detection of SLMP with a poor prognosis, DNA cytophotometry has been shown to be very helpful. Because the type of the peritoneal implants is of utmost prognostic importance, the WHO recommends evaluation of the peritoneal implants independently of the ovarian tumor. The molecular data on this topic will be discussed in part 2 of this serial paper.

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