Virchows Archiv A Pathol Anat (1992) 421:497–503

Virchows Archiv A
Pathological Anatomy and Histopathology

DNA-cytophotometry and immunocytochemistry in ovarian tumours of borderline malignancy and related peritoneal lesions*

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Received May 15, 1992 / Received after revision and accepted August 10, 1992

Summary. A total of 34 surgical specimens, obtained from 13 patients with ovarian tumours of borderline malignancy (OTBM), were investigated by conventional histology, immunocytochemistry and DNA cytophotometry. The lesions were obtained by primary ovarian surgery or second-look procedures and altogether comprised 19 (single and bilateral) OTBM, 8 cases of endosalpingiosis, 4 in situ and 2 invasive peritoneal implants and 1 overt adenocarcinoma. The morphological findings were related to follow-up data, which showed neoplasms with clinically malignant behaviour in 2 patients. The histology of the extra-ovarian manifestations was not associated with their immunocytochemical properties or with their DNA content. There were no correlations between the evolution of disease and microscopical features but the clinical course appeared to be linked to the DNA content of the extra-ovarian lesions, which was of greater prognostic importance than DNA ploidy of the ovarian tumours. Recurrence-free survival was noted in all 5 patients with diploid or euploid extra-ovarian proliferations, while the 2 clinically malignant cases fell into the group of 3 patients with noneuploid or aneuploid specimens. DNA estimations may be a methodology which increases the prognostic value of second-look procedures in OTBM patients.

Key words: Ovarian tumours of borderline malignancy – Peritoneal implants – DNA cytophotometry – Immunocytochemistry

Introduction

The common epithelial tumours of the ovary represent neoplasms derived from the müllerian surface epithelium of the gonads. Histologically, the three categories, adenoma, ovarian tumour of borderline malignancy (OTBM), and carcinoma are recognized, each of which can be subclassified into serous and mucinous lesions (Katzenstein et al. 1978; Blaustein 1981; Colgan and Norris 1983). OTBM, amounting to approximately 15% of all cases, is defined – in the absence of stromal invasion – by the presence of any two of the following four features: epithelial budding, multilayering of the epithelium, increased mitotic activity and nuclear atypia (Russell 1984). The diagnosis is based on the histological findings of the ovarian neoplasm only (Serov et al. 1973; Hart 1977), although 30–50% of women with serous OTBM exhibit proliferations of müllerian epithelium at extra-ovarian peritoneal sites (Russell et al. 1985; Bell and Scully 1990). In many of these instances it is not clear whether the peritoneal lesions represent true metastases from an ovarian primary rather than autochthonous proliferations of the peritoneal mesothelium. The latter have been assumed to arise in the pelvic or abdominal cavity as a result of multifocal tumorigenesis involving metaplastic coelomic epithelium that has retained some müllerian potential (Russell et al. 1985). Alternatively, sloughing and peritoneal inclusion of tubal epithelium have been considered as a possible aetiology for these findings (Schuldenfrei and Janovski 1962; Kheir et al. 1981; Zinsser and Wheeler 1982). Irrespective of their concrete histogenesis, the prognostic impact of such peritoneal lesions is still a matter of debate (Russell 1984; McCaughey 1985; Michael and Roth 1986; Bell et al. 1988). The aim of the present study therefore was to relate histological, immunocytochemical and DNA cytophotometrical data of patients with OTBM and extra-ovarian proliferations of müllerian epithelium to the further evolution of disease.

Materials and methods

The series comprised 13 patients in whom at least one further proliferation of müllerian epithelium was documented in addition to

* Supported by grants from the Hamburger Krebsgesellschaft and the Hamburger Gesellschaft zur Förderung der Krebsbekämpfung

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OTBM, either upon initial surgery or during second-look procedures. Formalin-fixed paraffin-embedded material of 34 different manifestations (on average, one block per 1 cm of maximal OTBM size and one block per 0.5 cm of diameter of a given extra-ovarian lesion) was available for study. In each patient, the development of disease following primary surgery was documented until spring 1992 (observation period: median 3, mean 3.8, range 1–12 years).

Histological reclassification and staging of OTBM were performed as indicated by the World Health Organization (Serov et al. 1973) and the Oncology Committee of the International Federation of Gynecology and Obstetrics (FIGO) (1987), respectively. Peritoneal lesions were classified histologically according to the criteria laid down by Michael and Roth (1986) and Bell et al. (1988). Utilizing the ABC method (Hsu et al. 1981), antibodies against cytokeratin (KL-1 – species: mouse; source: Immunotech; dilution: 1:200, MA-902 and MA-903 – mouse, Enzo, 1:500 and 1:1000, respectively), epithelial membrane antigen (EMA; goat, Sera-Lab, 1:100), vimentin (mouse, Boehringer Mannheim, 1:20), Leu-M1 (mouse, Becton Dickinson, 1:50), chromogranin A (mouse, Hybritech, 1:500), serotonin (mouse, Camon, 1:500), histamine (rabbit, Milab/IBL, 1:5), lysozyme (rabbit, Biogenex, 1:5), carcinoembryonic antigen (CEA; 431/31, mouse, Behring, 1:3), CA 125 and CA 19–9 (each Histo-Cis, mouse, 1:5) were applied. DNA cytophotometry, analysing 50–100 cells for each lesion, was performed as described elsewhere (Padberg et al. 1990). Diploid values were obtained from normal ovarian stroma cells; the mean ± 2 SD of their nuclear DNA content was defined as the 2c region. The data were evaluated by classifying the DNA histograms into four different types (I–IV; see Results for details), according to the methods of Auer et al. (1980).

Results

A summary of clinical, histological and DNA cytophotometrical data is given in Table 1. At primary surgery, the mean patient age was 45 years (median 42, range 25–75 years). Surgical treatment for OTBM consisted of either total hystero-oophorectomy with or without omentectomy ($n=9$) or unilateral adnexectomy with or without wedge resection of the contralateral ovary ($n=3$). Patient 13 had bilateral wedge resection only, because preservation of fertility was desired. In patients 5 and 11, chemotherapy was applied after second-look procedure.

Among the 13 patients, a total of 19 OTBM was found. The tumours ranged from 1 to 23 cm (median 8.0, mean 8.8 cm) in diameter and were unilateral in 7 and bilateral in 6 cases. Histologically 18 of the tumours were classified as serous and 1 as mucinous (patient 4). At primary surgery, 3 patients (nos. 4, 7 and 8) showed tumours confined to one ovary. In the remaining cases, surface involvement of one or, in the case of bilateral OTBM, both ovaries (Fig. 1a) and microscopic extra-ovarian pelvic (patients 1, 2 and 12) and/or extrapelvic (patients 1 and 6) proliferations were found. Histologically, all extra-ovarian lesions (including all manifestations seen at later interventions) were of the serous cell type. In 3 of the 4 afflicted patients (nos. 1, 2 and 6), they exhibited benign glands lined by a single layer of tubal-type epithelium without nuclear atypia and were typed as *endosalpingiosis* (Fig. 1b). In the fourth case (patient 12), a (non-invasive) *in situ implant* was diagnosed, since microscopy showed glandular structures resembling OTBM in that the proliferations demonstrated mild to moderate nuclear pleomorphism, but were confined by intact basement membranes (Fig. 1c, d).

All 13 patients were subjected to second-look surgery, which demonstrated peritoneal lesions in 8 cases. Among these, endosalpingiosis occurred in 4 patients (nos. 1, 10, 11 and 13), while 3 cases showed in situ implants (patients 2, 6 and 12). Patient 5 exhibited an *invasive implant*, which histologically was characterized by irregular glands with severe nuclear atypia associated with desmoplastic stroma and a poorly demarcated gland-stromal interface (Fig. 1e, f).

Third-look procedures were carried out in 4 patients. Negative findings were recorded in 2 cases. In the remaining 2 patients, histology showed an invasive peritoneal implant (patient 5) and a para-iliac lymph node metastasis of moderately differentiated papillary adenocarcinoma (patient 13), respectively.

One patient (no. 11) was subjected to fourth- and fifth-look interventions, which were negative each time.

At the end of the observation period, 11 patients showed continuous symptom-free survival. The patient with previously documented nodal spread (no. 13) was alive with persistent tumour manifestations 17 months after primary surgery, while patient 5 had died from diffuse intra-abdominal tumour dissemination 59 months following initial treatment.

Immunocytochemically, all 34 lesions uniformly showed strong reactivity (more than 50% of cells being decorated) for cytokeratin and EMA and were entirely devoid of staining for chromogranin A, histamine and serotonin. Strong positive staining for CEA was seen only with the solitary mucinous OTBM. Immunostaining for vimentin, CA 19-9, CA 125, Leu-M1 and lysozyme consistently produced negative results in each series of four different specimens of 2 patients (nos. 1 and 5). Moderate reactivity (between 20% and 50% of positive cells) for the latter antigens was seen with several of the remaining manifestations (vimentin $n=14$, CA 19-9 $n=13$, CA 125 $n=11$, Leu-M1 $n=11$ and lysozyme $n=5$). As shown in Table 1, the staining pattern varied from case to case and lacked any evident association with the histological type of disease.

Upon DNA cytophotometry of the altogether 19 (uni- and bilateral) OTBM, 2 cases showed (diploid) type I histograms characterized by a single peak of diploid DNA values as found in control cells (Fig. 2a). In 7 lesions, (euploid) type II histograms were recorded demonstrating two well-defined peaks around the 2c and 4c regions (Fig. 2b). Nine OTBM exhibited (noneuploid) type III histograms differing from the aforementioned cases in that a sizeable amount of cells had DNA values between 2c and 4c (Fig. 2c). In 1 tumour, a (aneuploid) type IV histogram was documented, which displayed a very pronounced and irregular aneuploidy with DNA amounts per cell ranging from levels near 2c up to 10c (Fig. 2d).

Among the total of 8 endosalpingioses removed during primary surgery or documented upon later interventions, 1 type I, each 3 type II and type III and 1 type IV DNA histogram was seen. Of the altogether 4 in situ

Table 1. Summary of clinical and morphological findings in 13 patients with ovarian tumours of borderline malignancy (OTBM)

Patient no.	Age (years)	Surgical procedure and interval (months)	Location, diameter (cm), histological diagnosis and FIGO stage of disease			Immunocytochemistry					Type of DNA histogram	Follow-up period (months) and outcome
						Vimentin	CA 19-9	CA 125	Leu-M1	Lysozyme		
1	56	Primary surgery	Right ovary	6.0	OTBM, FIGO IC	−	−	−	−	−	III	31 NED
			Omentum		Endosalpingiosis	−	−	−	−	−	III	
			Pelvic periteneum		Endosalpingiosis	−	−	−	−	−	III	
		2nd Lood 6	Pelvic peritoneum		Endosalpingiosis	−	−	−	−	−	III	
2	48	Primary surgery	Right ovary	14.0	OTBM, FIGO IC	−	+	+	−	−	III	20 NED
			Left ovary	13.0	OTBM	−	+	+	+	−	III	
			Douglas		Endosalpingiosis	−	+	+	−	−	II	
		2nd Look 9	Omentum		In situ implant	−	+	+	−	−	I	
3	38	Primary surgery	Left ovary	12.0	OTBM, FIGO IC	+	−	−	−	+	II	36 NED
			Right ovary	3.5	OTBM	−	−	−	−	−	II	
		2nd Look 6			Negative							
4	50	Primary surgery	Right ovary	23.0	OTBM, FIGO IA	−	+	−	−	+	II	45 NED
		2nd Look 13			Negative							
5	62	Primary surgery	Left ovary	10.0	OTBM, FIGO IC	−	−	−	−	−	III	59 DFT
			Right ovary	9.0	OTBM	−	−	−	−	−	III	
		2nd Look 46	Pelvic peritoneum		Invasive implant	−	−	−	−	−	IV	
		3rd Look 58	Pelvic peritoneum		Invasive implant	−	−	−	−	−	IV	
6	39	Primary surgery	Left ovary	8.0	OTBM, FIGO IC	+	−	−	+	−	IV	85 NED
			Right ovary	8.0	OTBM	+	+	−	−	−	II	
			Omentum		Endosalpingiosis	+	−	−	−	−	II	
		2nd Look 9	Pelvic peritoneum		In situ implant	+	−	−	−	−	II	
7	60	Primary surgery	Left ovary	8.0	OTBM, FIGO IA	+	+	−	+	−	III	145 NED
		2nd Look 32			Negative							
8	42	Primary surgery	Right ovary	10.0	OTBM, FIGO IA	−	+	−	+	−	III	30 NED
		2nd Look 30			Negative							
9	75	Primary surgery	Right ovary	7.5	OTBM, FIGO IC	+	+	−	+	−	III	12 NED
		2nd Look 12			Negative							
10	35	Primary surgery	Right ovary	5.0	OTBM, FIGO IC	−	−	+	−	−	I	36 NED
			Left ovary	3.0	OTBM	−	−	+	−	−	I	
		2nd Look 4	Abdominal peritoneum		Endosalpingiosis	−	−	−	−	−	I	
11	25	Primary surgery	Right ovary	1.0	OTBM, FIGO IC	+	+	+	+	+	II	73 NED
		2nd Look 3	Abdominal peritoneum		Endosalpingiosis	+	+	+	+	+	II	
		3rd Look 6			Negative							
		4th Look 40			Negative							
		5th Look 48			Negative							
12	31	Primary surgery	Right ovary	5.2	OTBM, FIGO IIB	+	−	−	−	−	II	12 NED
			Left ovary	3.5	OTBM	+	−	−	−	−	II	
			Pelvic peritoneum		In situ implant	+	−	+	+	−	II	
		2nd Look 4	Pelvic peritoneum		In situ implant	−	−	−	+	−	I	
		3rd Look 11			Negative							
13	27	Primary surgery	Left ovary	3.5	OTBM, FIGO IC	+	+	+	−	−	III	17 AWT
		2nd Look 5	Pelvic peritoneum		Endosalpingiosis	+	−	−	+	−	IV	
		3rd Look 11	Para-iliac lymph node		Carcinoma	−	+	+	+	+	IV	

NED, No evidence of disease; DFT, death from tumour; AWT, alive with tumour

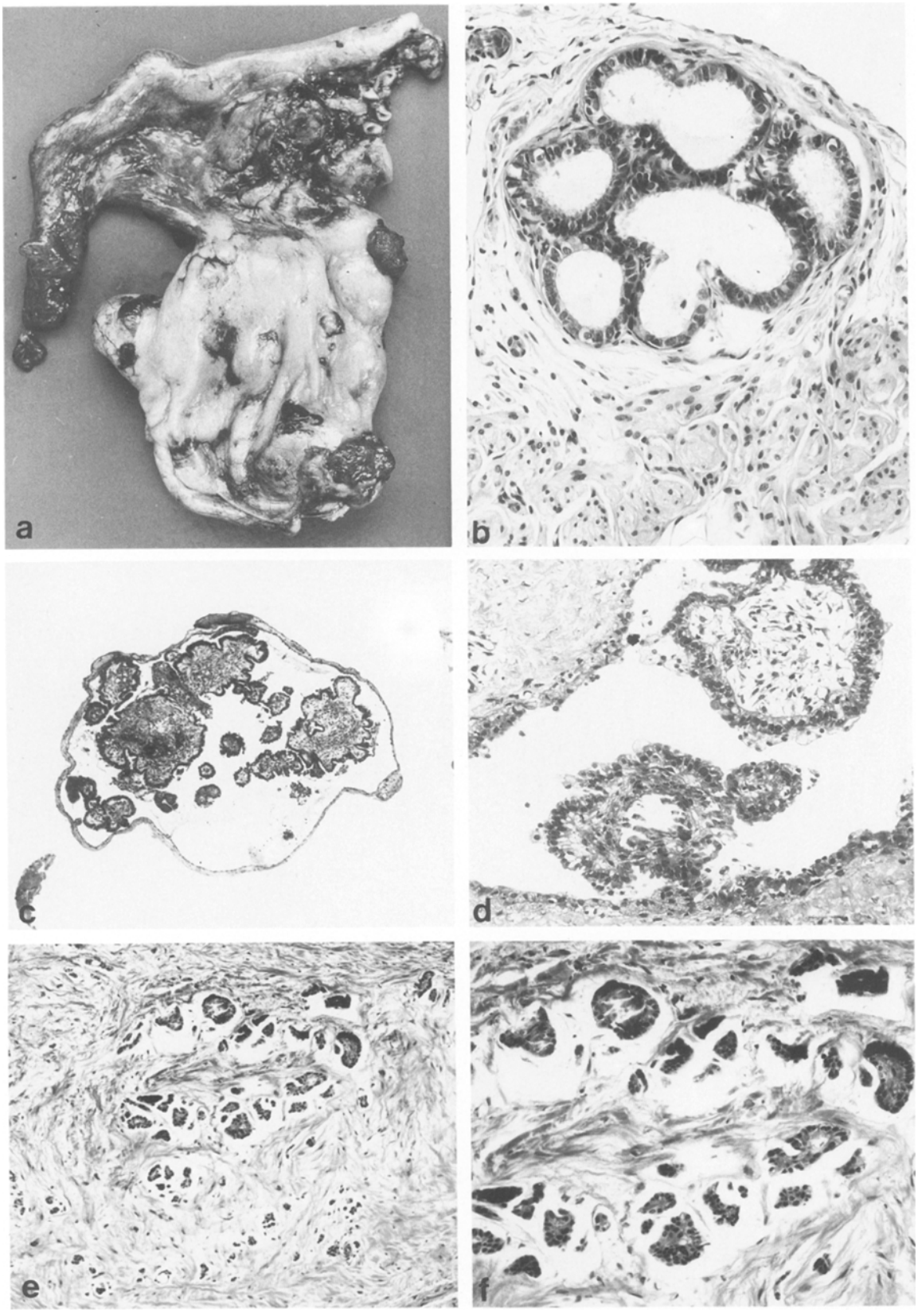

Fig. 1. a Macroscopic view of ovarian tumour of borderline malignancy (OTBM) showing multifocal surface involvement (patient 12). **b** Endosalpingiosis from the large omentum: glandular structures lined by epithelium of tubal type without nuclear atypia (patient 1). H & E, ×250 **c, d** In situ implant from the pelvic peritoneum: papillary and cystic proliferations consisting of multilayered epithelium with moderate nuclear pleomorphism (patient 12). H & E, ×50 and ×200, respectively. **e, f** Invasive implant from pelvic peritoneum: small clusters and irregular microtubular or trabecular formations of pleomorphic epithelial cells scattered within desmoplastic, partly myxoid stroma (patient 5). H & E, ×100 and ×200, respectively

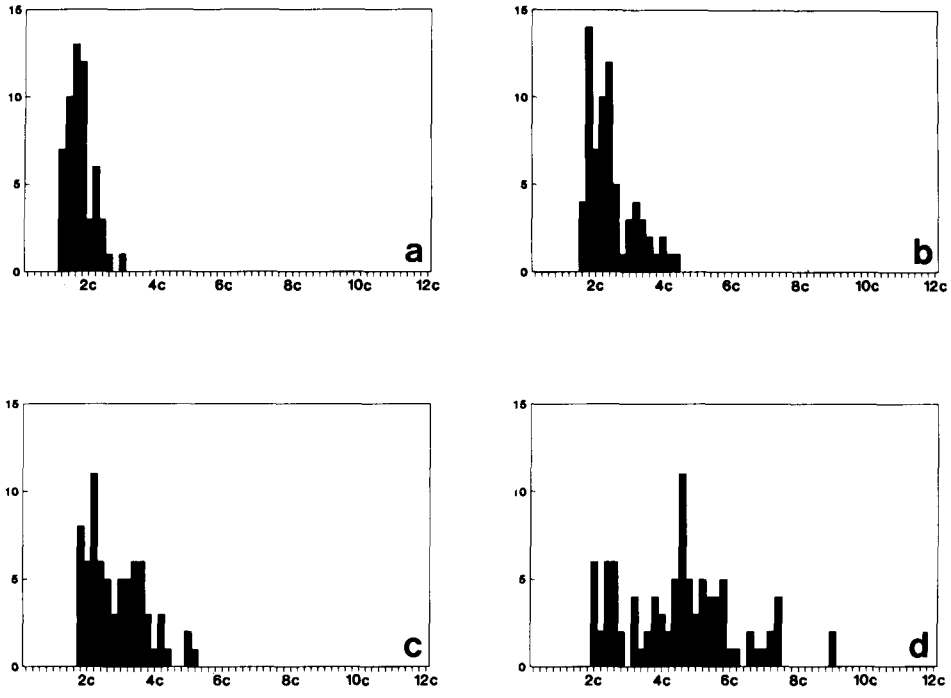

Fig. 2. Examples of typical DNA histograms: **a** type I, diploid (in situ implant from patient 2); **b** type II, euploid (OTBM, patient 4); **c** type III, non-euploid (OTBM, patient 13); **d** type IV, aneuploid (left-sided OTBM, patient 6)

implants, 2 cases each exhibited type I or type II DNA distributions, respectively. Type IV histograms were recorded for the 2 cases of invasive implant and for the single instance of lymph node infiltration by adenocarcinoma.

Discussion

The term endosalpingiosis was first coined by Sampson (1930) to define extra-ovarian glandular lesions which histologically resemble epithelium of normal endosalpinx and are devoid of surrounding endometrial stroma. Such inclusions may occur at different sites of the abdominal peritoneum and in retroperitoneal lymph nodes (Kempson 1978; Ehrmann et al. 1980; Kheir et al. 1981; Zinsser and Wheeler 1982; Shen et al. 1983; Dienemann and Pickartz 1987) and are capable of neoplastic transformation. Overt malignant change in endosalpingiosis appears to be a rare event (Zinsser and Wheeler 1982). More frequently patients are described with primary papillary peritoneal neoplasia of low malignant potential. This, in the absence of ovarian involvement, may occupy the entire abdominal cavity and cause ascites (Dallenbach-Hellweg 1987). If this type of disease, regardless of extent, is accompanied by an OTBM, the question arises as to whether the former has arisen autochthonously in a temporal relation to the ovarian tumour or whether it represents metastatic spread of the ovarian primary (Dienemann and Pickartz 1987). Another dilemma regards the biological potential of the extra-ovarian lesions. Several authors have addressed these problems by defining different histological types of peritoneal manifestations of müllerian epithelium, namely endosalpingiosis, in situ implant and invasive implant. The prognostic value attributed to this morphological approach (Russel 1984; McCaughey 1985; Bell et al. 1988) has, however, been disputed by others (Michael and Roth 1986) and appears doubtful in the light of our findings, since we failed to detect clear-cut discrepancies in the behaviour of these three types on review of the original slides after the completion of data collection.

Few immunocytochemical studies have been performed on ovarian tumours together with their related peritoneal proliferations (van Nagell et al. 1978; Dienemann and Pickartz 1987; Manivel et al. 1989; Ghazizadeh et al. 1990; Cajigas et al. 1991). Our results, obtained by utilizing a panel of 12 different antibodies, parallel the findings of others in that this technique lacks prognostic efficacy. The expression rates of vimentin, CA 19-9, CA 125, Leu-M1 and lysozyme, detected in variable combinations in 15–41% of the 34 specimens investigated herein, were neither associated with certain histological types nor with the further evolution of disease. Positive immunostaining with the CEA-specific antibody was restricted to the solitary mucinous tumour of our series, while the remaining antisera used, recognizing different cytokeratin subtypes, EMA, chromogranin A, serotonin and histamine, consistently produced predictable positive or negative results. Each of these probes thus lacked prognostic efficacy. It has, however, to be noted that we, in contrast to Dabbs and Geisinger (1988), but in accordance with Moll et al. (1991), also found antibodies against high-molecular-weight cytokeratins to be a sensitive method of characterizing the epithelial phenotype of müllerian epithelium proliferations. Both this phenomenon and the frequent positivity of such lesions for various carbohydrate antigens (including CEA, CA 19-9, CA 125 and Leu-M1)

have to be placed in the context of the differential diagnosis of peritoneal neoplasms, since genuine mesotheliomas have been shown to be negative with the relevant immunocytochemical probes (Dienemann and Pickartz 1987; Manivel et al. 1989; Vortmeyer et al. 1991).

The obvious limitations of microscopical procedures in predicting the behavior of extra-ovarian manifestations of müllerian epithelium led us to investigate whether DNA cytophotometry could help to identify individual neoplasms with aggressive potential. In accordance with other investigators, we have shown that the DNA content of the ovarian primery is an important independent prognostic indicator for OTBM (Friedlander et al. 1984; Fu et al. 1986; Padberg et al. 1992). There is, however, increasing evidence that aneuploidy of peritoneal lesions is another, if not the most significant, determinant for an aggressive course in individual OTBM cases. As far as we have been able to ascertain, only one other group has as yet communicated DNA findings of ovarian primaries and peritoneal proliferation in OTBM patients (Bell et al. 1989). Using DNA flow cytometry on paraffin-embedded material, these authors recorded death from tumour in 2 of 12 patients with diploid implants and in 1 of 2 patients with aneuploid disease. It was thus suggested that OTBM patients with aneuploid peritoneal proliferations have a somewhat greater risk of lethal outcome than those with diploid manifestations. Such conclusions are confirmed from our observations by taking together the DNA histograms of all extra-ovarian specimens, obtained from an individual patient upon primary surgery or during later interventions. This results in a clear-cut correlation between the DNA content of related extra-ovarian lesions and the clinical course; tumour recurrence or death resulting from tumour occurring in only 2 (nos. 5 and 13) of the 3 patients (nos. 1, 5 and 13) with noneuploid or aneuploid (types III or IV) disease, and in none of the 5 patients (nos. 2, 6, 10, 11 and 12) exhibiting diploid or euploid (types I or II) specimens. In contrast, the microscopic aspect of the extra-ovarian proliferations was correlated neither to their DNA content nor, as has to be re-emphasized in this context, to the outcome of disease.

In spite of the small number of cases, our results suggest that noneuploidy or aneuploidy in the ovarian primary alone is not associated with poor prognosis, as long as related peritoneal lesions show diploid or euploid DNA distributions. This assumption is supported by our observations in patients 2 and 6, who exhibited noneuploid or aneuploid OTBM, yet euploid or diploid peritoneal proliferations (FIGO stage IC) and both showed recurrence-free survival at the end of observation period. With respect to the discrepancies in DNA content between ovarian and extra-ovarian lesions we may speculate that at least in these 2 cases the peritoneal manifestations, regardless of their histological aspect, represented benign autochthonous müllerian proliferation rather than metastases of ovarian OTBM. This may be the reason why DNA content of the extra-ovarian lesions appeared to be of higher prognostic importance that DNA ploidy of the ovarian tumours.

The most appropriate therapeutic strategy and the utility of second-look interventions (Copeland et al. 1985; Nation and Krepart 1986) in OTBM patients is still a matter of debate. Several outhors have doubted the efficacy of adjuvant therapeutic procedures for this type of disease (Hart and Norris 1973; Creasman et al. 1982; Kliman et al. 1986), while others suggested unilateral (salpingo-)oophorectomy to be sufficient in early stage OTBM occurring in the reproductive age group (Julian and Woodruff 1972; Russell and Merkur 1979; Nikrui 1981; Kjörstad and Abeller 1983; Tazelaar et al. 1985; Yoonessi et al. 1988). This recommendation is not supported by a review of the treatment performed in OTBM patients (Padberg et al. 1992). Eighty-two percent of 256 patients included in four different studies were subjected to extensive surgery (including bilateral adnexectomy and hysterectomy) and 33% to radiation and/or chemotherapy.

We have found DNA estimations of extra-ovarian proliferations related to OTBM, obtained upon primary surgery and during later interventions, to be the most effective means of discriminating between high-risk and low-risk neoplasms. This underlines the prognostic usefulness of second-look procedures, and requires DNA measurements to be included in the diagnostic process on principle. If diploid or euploid values are recognized, the findings, like unilateral occurrence of OTBM (Julian and Woodruff 1972; Nikrui 1981) can be regarded as a criterion to recognize low-risk patients which can be managed safely by a conservative therapeutic approach.

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