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Minimal uterine serous carcinoma: a clinicopathological study of 40 cases

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The term 'minimal uterine serous carcinoma' has been proposed to include serous carcinomas with invasion limited to the endometrium (superficial serous carcinoma), and those without stromal invasion (intraepithelial serous carcinoma or endometrial intraepithelial carcinoma). Both lesions display similar cytological and immunohistochemical profiles of a typical invasive serous carcinoma with a high nuclear grade and an overexpression of mutant p53 protein. We studied the clinicopathologic features of 40 cases of minimal uterine serous carcinoma. All patients were postmenopausal and underwent hysterectomy and surgical staging procedures. There were nine cases of intraepithelial serous carcinoma and 31 cases of superficial serous carcinoma. Five intraepithelial serous carcinomas and 16 superficial serous carcinomas exclusively involved an endometrial polyp. A total of 18 minimal uterine serous carcinomas also involved, in addition to a polyp, the endometrium proper in the form of intraepithelial serous carcinoma (13 cases) and superficial serous carcinoma (five cases). Overall, minimal uterine serous carcinomas were found to involve an endometrial polyp in 88% of the cases (35/40) and were confined to the polyp in 53% (21/40). Extrauterine tumors were present in 45% of the cases (18/40). In all, 22 patients with tumor limited to their uteri demonstrated an overall survival of 94% (2–73 months of follow-up). Eight of 18 patients with extrauterine tumors died of their malignancy (1.5–62 months of follow-up). In conclusion, a significant majority of minimal uterine serous carcinomas involve an endometrial polyp. Complete surgical staging is important to predict the prognosis. When the lesion is confined to an endometrial polyp and/or the endometrium proper, the clinical outcome is excellent.
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Uterine serous carcinoma is a major histological subtype of endometrial epithelial malignancy. In contrast to more common endometrioid carcinoma, little is known about the etiology, precursor lesion and population at risk for uterine serous carcinoma. Recent histological and clinical studies have identified a few pathological entities classified as 'intraepithelial serous carcinoma' by us or 'endometrial intraepithelial carcinoma' (EIC) by others[1,2] and 'superficial serous carcinoma',[1–3] representing the noninvasive intraepithelial and early invasive stages of uterine serous carcinoma, respectively. Both lesions display similar cytological and p53 immunohistochemical profiles of a full-blown serous carcinoma. The term 'minimal uterine serous carcinoma' has been suggested to include the two entities.[1] Studies of such early carcinomatous changes are important as the background endometrium may harbor pre-neoplastic alterations, especially precursor lesions or benign lesions in transformation. However, pathological and clinical studies of minimal uterine serous carcinoma have been limited to a few reports. Additional studies are prudent to expand our knowledge in this area. In an effort to identify precursor lesions and to refine pathological staging in correlation with clinical outcome, a study of 40 cases of minimal uterine serous carcinoma is reported here, reflecting the largest series to date.

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Materials and methods

Case Selection

A text search of Yale's surgical pathology files from 1985 through 2003 was performed with a final

diagnosis of serous carcinoma of endometrium, endometrial intraepithelial carcinoma or endometrial malignancy with serous carcinoma features. The study was limited to cases surgically staged with hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection and/or omental sampling. Two cases, likely reported previously,[4] were included in this study (Table 1, cases #19 and #23). Hematoxylin- and eosin (H&E)-stained sections of each case (15–48 slides per case) were reviewed. Tumors of mixed histological types (endometrioid, clear cell, and carcinosarcoma) were excluded.

Cases of minimal uterine serous carcinoma were eventually identified based on the published histopathologic criteria.[1,3] Intraepithelial serous carcinoma or 'endometrial intraepithelial carcinoma' was defined as a replacement of surface epithelium and/or underlying glands of the endometrium or an endometrial polyp by a flat (Figure 1a) or micropapillary (Figure 1b) proliferation of cells resembling serous carcinoma, and stromal invasion is absent. The neoplastic cells usually have scanty cytoplasm with high nuclear-to-cytoplasmic ratio, marked nuclear pleomorphism, hyperchromasia, and eosinophilic macronucleoli. Mitotic figures are easily found with frequent abnormal forms. Superficial serous carcinoma is defined as a serous carcinoma with early stromal invasion characterized by either confluent glands (Figure 1c) or an infiltrative growth associated with desmoplasia (Figure 1d). The invasion is focal and confined to an endometrial polyp or endometrium proper, without myometrial invasion. An endometrial polyp is defined histologically as a focal proliferation of endometrium in a polypoid configuration along with sclerosing stroma and thickened wall vessels. Minimal uterine serous carcinoma involving an endometrial polyp was defined as intraepithelial or superficial serous carcinoma replacing a portion of an endometrial polyp. Cases with myometrial invasion and/or lymphovascular involvement were excluded.

Immunohistochemistry

Since overexpression of mutant p53 protein has become a surrogate marker for uterine serous carcinoma,[5] p53 immunohistochemistry was performed in 37 cases. The staining was not performed in three cases where blocks were not available. Scoring of the p53 staining was carried out according to an established method,[6] using a 0- to 3-point score for the percentage of cells staining (0: $<10\%$; 1: 10–25%; 2: 26–50%; and 3: $>50\%$), intensity (1: weak; 2: moderate; and 3: strong) and heterogeneity (1: marked; 2: moderate; and 3: mild to none), resulting in a range of total scores from 0 to 9 points. A score of 7 or above was considered characteristic for serous carcinoma (Figure 2b).

Follow-up Information

Follow-up data were obtained by reviewing medical records of the patients and by contacting referring clinicians. Surgical staging was accomplished according to the International Federation of Gynecology and Obstetrics 1988 publication. Kaplan–Meier survival curves were generated in cases with available follow-up data according to clinical stages (stages I/II and III/IV).

Results

Clinical Findings

A total of 331 cases of uterine serous carcinoma or carcinoma with serous component were found in the pathology files at Yale-New Haven Hospital from 1985 through 2003, among which 40 consecutive cases of minimal uterine serous carcinoma (Table 1) fulfilling the criteria defined above were eventually identified. The average age of presentation was 67.0 years. In all, 15 patients with a low-stage tumor (FIGO stages I and II) presented with postmenopausal bleeding. Eight of 18 patients with high stage tumor (FIGO stages III and IV) presented with abdominal distension. The rest of high-stage patients were found to have extrauterine disease based on histopathological evaluation. Three patients had breast cancer history and had received tamoxifen therapy. A revisit of patients' pap smear and biopsy history was made and the relevant information was given in Table 1. A total of 27 patients did not have a pap smear prior to the diagnosis of serous carcinoma. Seven patients had a positive biopsy or curettage simultaneously with or immediately following a positive pap (positive for malignant cells). Six patients had a negative pap smear at the same time or prior to a positive biopsy and the intervals varied from 0 to 6 months.

Gross Pathologic Finding in Hysterectomy Specimen

A gross description of hysterectomy specimen was available in all cases. The size of the uteri ranged from 4.5 to 12.0 cm (a measurement from fundus to ectocervix in 31 cases). An endometrial polyp was grossly identified in 70% of the cases (28/40). The polyps ranged in size from 0.4 to 7.5 cm. Multiple endometrial polyps were present in four cases. In all, 15 cases had one or multiple intramural leiomyomas, while three cases showed submucosal leiomyomas. The nonpolyp endometrial surface was unremarkable in most cases; however, four cases were described as focal nodular, papillary or thickened. Except for the endometrial polyp and submucosal leiomyoma, no other gross endometrial lesions were identified in any of the uteri. The endocervix was unremarkable in all cases, except for an endocervical polyp in one.

Table 1 Clinicopathological features of minimal uterine serous carcinoma ($n = 40$ cases)

#	*Age*	*Presentation*	*Pap*	*Biopsy/ curettage*	*Uterus (cm)*	*Polyp size (cm)*	*Tumor endometrial polyp*	*Tumor endometrium proper*	*Extrauterine dis*	*Stage*	*P53 score*	*Survival F/U (mo)*	*Status*
1	49	Cervical HPV	HPV	EMB+	6.5		Benign polyp	ISC	No	IA	0	64	Alive/NED
2	64	PMB	ND	EMC+	12	2.7, 2.3	ISC	No	No	IA	9	1	Alive/NED
3	61	PMB	ND	EMC+	5.5	0.4, 0.9, 4.5	ISC	No	No	IA	9	5	Alive/NED
4	68	PMB	ND	EMC+		6.5,3.5	ISC	No	No	IA	9	9	Alive/NED
5	73	Pap(+)	NEG	EMB+	6	1.7	ISC	No	No	IA	0	27	Alive/NED
6	72	PMB	NEG	EMC+	5		No polyp	ISC	No	IA	7	41	Alive/NED
7	56	ABD	ND	Peritoneal BX+	9.2	0.9	Benign polyp	ISC	Yes	IVB	7[a]	22	Alive/with Disease
8	71	Pap(+)	POS	EMB+	8.2	2.9	ISC	No	Yes	IVB	8	26	Dead of Disease
9	76	ABD	ND	No prior specimen	10		No polyp	ISC	Yes	IVB	7[a]	62	Dead of disease
10	67	PMB	NEG	EMB+	7	1.5, 1.2	ISC, SSC	No	No	IA	9	55	Alive/NED
11	68	PMB	ND	EMC+	5	2.5	ISC, SSC	No	No	IA	7	13	Alive/NED
12	73	PMB	ND	EMB+	6.5	3	ISC, SSC	ISC	No	IA	9	25	Alive/NED
13	54	PMB	POS	EMC+	7.5	1.7	ISC, SSC	ISC	No	IA	9	8	Alive/NED
14	56	PMB	ND	EMB+	7		ISC, SSC	No	No	IA	5	51	Alive/NED
15	57	PMB	ND	EMC+	4.5	1.2	ISC, SSC	No	No	IA	0	67	Alive/NED
16	58	Unknown	ND	EMB+	9.5		ISC, SSC	No	No	IA	ND	34	Alive/NED
17	58	PMB	ND	EMC+	7		ISC, SSC	No	No	IA	ND	47	Alive/NED
18	71	Pap(+)	POS	EMB+	8	2.9	ISC, SSC	No	No	IA	7	25	Alive/NED
19	72	PMB	ND	EMC+	10	3	ISC, SSC	No	No	IA	7	26	Lost/NED
20	75	PMB	ND	EMC+	9	2	ISC, SSC	No	No	IA	3	26	Alive/NED
21	83	Unknown	ND	EMB+	7.7	1.5	ISC, SSC	No	No	IA	8	—	Lost follow-up
22	63	Pap(+)	POS	EMC+			ISC/SSC	ISC	No	IA	ND	14	Alive/NED
23	69	PMB	ND	EMC+	7.5		SSC	ISC	No	IA	8	—	Lost follow-up
24	52	Unknown	ND	EMC+	8.5	2.5	ISC, SSC	ISC	No	IIA	3	27	Lost/NED
25	68	PMB	ND	EMC+	8	5.5	ISC, SSC	ISC	No	IIA	0	23	Dead of disease
26	80	PMB	ND	EMB+	8		ISC, SSC	No	Yes	IVB	7[a]	12	Alive/NED
27	70	PMB	ND	EMC+	7	2.7	ISC, SSC	ISC	Yes	IIIA	9	17	Alive/NED
28	70	Pap(+)	POS	EMC+	9.3	1	ISC, SSC	ISC, SSC	Yes	IIIA	8	8	Alive/NED
29	67	ABD	ND	No prior specimen	8.5	1	ISC, SSC	No	Yes	IVB	9	7	Lost/NED
30	72	PMB	ND	No prior specimen	7.5		No polyp	ISC, SSC	Yes	IIIA	0	16	Dead of disease
31	52	Pap(+)	POS	EMC+	9		ISC, SSC	No	Yes	IIIC	6	60	Alive/NED
32	64	ABD	ND	No prior specimen	7.5	5	ISC	ISC, SSC	Yes	IVB	9	13	Dead of disease
33	63	Pap(+)	POS	EMB+	7	5.2	ISC, SSC	ISC	Yes	IVB	9	8	Alive with disease
34	65	ABD	ND	EMC+	8	1.3	ISC, SSC	ISC	Yes	IVB	0	19	Dead of disease
35	68	PMB	ND	EMC+	7.5	1	ISC, SSC	ISC, SSC	Yes	IVB	8	19	Dead of disease
36	74	ABD	ND	FNA/omentum+	10	2	ISC, SSC	ISC, SSC	Yes	IVB	0	14	Dead of disease
37	62	ABD	NEG	No prior specimen	9.5	1.4	ISC, SSC	No	Yes	IVB	0	27	Alive with disease
38	69	ABD	NEG	Paracentisis+	8	7.5	ISC, SSC	No	Yes	IVB	7[a]	1.5	Alive with disease
39	72	PMB	ND	EMC+	8.5	1.5	ISC, SSC	No	Yes	IVB	7	3	Dead another cause
40	77	Unknown	ND	EMB+	7.2		ISC, SSC	No	Yes	IVB	8	36	Dead of disease

PMB: postmenopausal bleeding; HPV: human papilloma virus; ABD: abdominal distension; ISC: intraepithelial serous carcinoma; SSC: superficial serous carcinoma; ND: not done; LN: lymph node; NED: no evidence of disease; EMB: endometrial biopsy; EMC: endometrial curettage; FNA: fine-needle aspiration.

[a]– p53 score is 7 or above. Pap (+)– Papanicolau smear is positive for malignant cells.

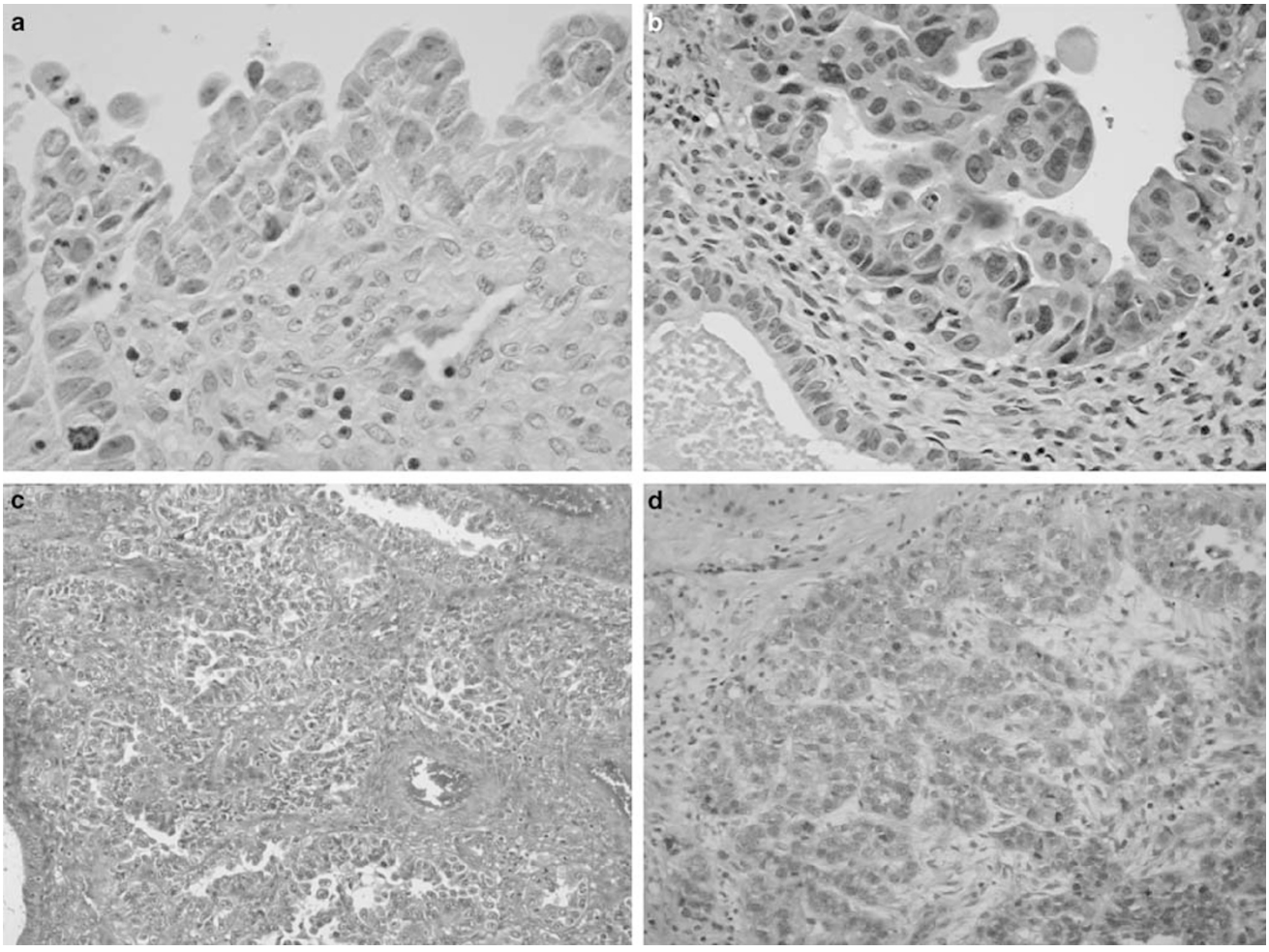

Figure 1 Histological and cytological features of minimal uterine serous carcinoma. The neoplastic cells are similar to those of a full-blown serous carcinoma with high nuclear-to-cytoplasmic ratio, nuclear hyperchromasia, pink cytoplasm and a variable number of eosinophilic nucleoli. Brisk mitotic activity with abnormal forms is frequently present. (**a**) intraepithelial serous carcinoma, flat pattern; (**b**) intraepithelial serous carcinoma, papillary pattern; (**c**) superficial serous carcinoma, confluent growth pattern; (**d**) superficial serous carcinoma, infiltrative growth associated with desmoplasia.

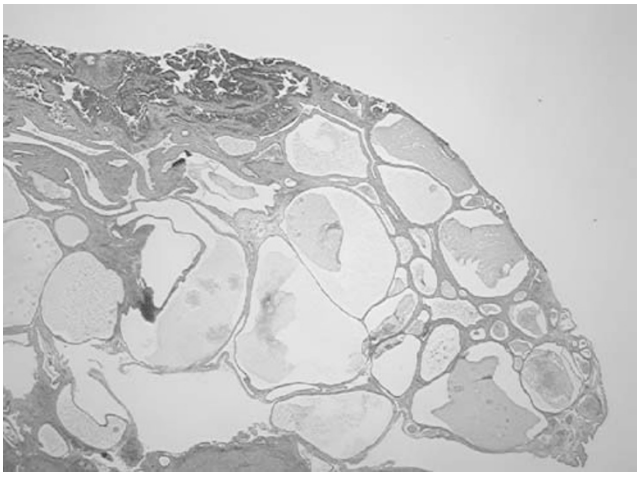

Figure 2 A portion of endometrial polyp involved (upper left) by minimal uterine serous carcinoma.

Histopathology and Immunohistopathology

Table 1 summarizes the clinical and pathological findings in this study. A total of 28 hysterectomy specimens demonstrated an endometrial polyp upon gross examination and an additional nine cases had histological evidence of polyp in their uteri or corresponding biopsy/curettage specimens. Three cases showed no evidence of endometrial polyp. Among 40 minimal uterine serous carcinomas, there were nine cases of intraepithelial serous carcinoma (Table 1, cases 1–9) and 31 cases of superficial serous carcinoma (Table 1, cases 10–40). Five of nine intraepithelial serous carcinomas involved exclusively an endometrial polyp. Among 31 cases of superficial serous carcinoma with or without intraepithelial serous carcinoma, the lesion was confined to an endometrial polyp in 16 patients. In all, 14 cases had superficial serous carcinoma

involving an endometrial polyp with an additional involvement of the endometrium proper, by intraepithelial serous carcinoma (10 cases) and superficial serous carcinoma (four cases). The foci of intraepithelial serous carcinoma involving the endometrium proper were mostly found in continuum with or adjacent to the polyp. However, in two cases, the intraepithelial lesion was extensive, involving multiple areas of the endometrium. When superficial serous carcinoma involved the endometrium proper, the lesions consisted of one-to-multiple microscopic foci (1.0–4.0 mm in size). In one case (Table 1, case 30), an endometrial polyp was not identified, but the endometrium was involved extensively by intraepithelial serous carcinoma with multiple foci of superficial serous carcinoma. Overall, minimal uterine serous carcinomas were found to involve an endometrial polyp in 88% of the cases (35 of 40). A total of 53% (21/40) showed that the carcinoma was confined to a polyp, and often only the surface of the polyp was involved (Figure 2). Diffuse overexpression of p53 with a score of 7 or above was seen in 68% of the cases (25/37), in which the immunostaining was performed.

Occasionally, epithelial alterations adjacent to a minimal serous carcinoma were observed within an endometrial polyp. These included cellular crowding, increased nuclear-to-cytoplasmic ratio and mild-to-moderate nuclear atypia. However, the level of the atypia did not reach to that of a minimal serous carcinoma (Figure 3). Such epithelial alterations were observed in a few cases in this study including one (Table 1, case 2) where an intraepithelial serous carcinoma was found at the tip of a large endometrial polyp. The adjacent glandular epithelium was found to have the aforementioned atypical changes (Figure 3a) with an additional demonstration of a diffuse p53 immunostaining similar to that of the adjacent intraepithelial serous carcinoma (Figure 3b).

Extrauterine Disease

Extrauterine tumor spread was found in 18 cases at the time of hysterectomy (Table 2). Of these 18 cases, 10 showed gross evidence of tumor deposits involving extrauterine organs, ranging from 0.5 cm to bulky lesions. The omentum was grossly involved in all 10 cases. No other site was identified to have gross disease when the omentum was grossly normal. Upon histological examination, extrauterine tumor deposits were found in an additional seven cases, consisting of microscopic tumor deposits involving ovarian surfaces and/or the omentum (five cases), or microscopic tumor on tubal and omental surfaces (one case), or micrometastasis to pelvic lymph node (one case). Of 17 cases, 13 were

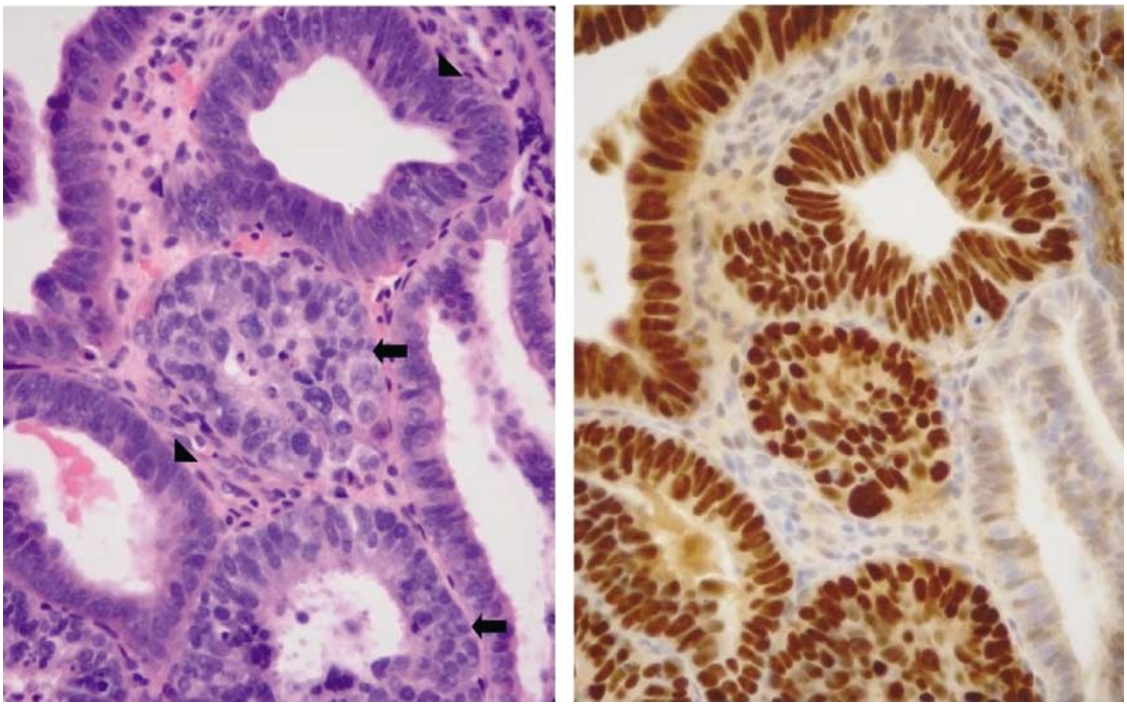

Figure 3 Epithelial alterations adjacent to minimal serous carcinoma. Left: intraepithelial serous carcinoma, flat pattern, involving two glands (arrows) with adjacent glandular epithelium showing moderate cytological atypia, while keeping an overall epithelial polarity (arrow heads). A benign endometrial gland is present at the lower right corner. Right: p53 immunohistochemical staining of the corresponding H&E section. Note: extensive nuclear staining of both intraepithelial serous carcinoma and adjacent glandular epithelium with moderate cytological atypia (p53 score of 9).

Table 2 Pathological findings of extrauterine disease of minimal uterine serous carcinoma ($n=18$)

Case #	*Ovary*	*Fallopian tube*	*Omentum*	*Pelvic peritonium*	*ABD organ surface*	*LN*	*Washing*
7	Surface/microscopic		Gross		Gross		Positive
8	Surface/microscopic	Surface/microscopic	Gross				Positive
9	Surface/microscopic		Gross		Gross		Positive
26	Surface/gross		Gross				ND
27	Surface/microscopic						Positive
28							Positive
29	Surface/microscopic		Gross	Gross			Positive
30	Surface/microscopic						Negative
31						Met	Negative
32			Microscopic	Microscopic		Met	Positive
33		Surface/microscopic	Microscopic				Negative
34			Microscopic			Met	Positive
35	Surface/microscopic	Surface/microscopic	Gross	Gross	Gross		Negative
36	Surface/microscopic	Surface/microscopic	Gross	Microscopic	Gross	Met	Positive
37		Surface/microscopic	Gross				Positive
38	Surface and parenchyma/gross		Gross	Gross	Gross	Met	Positive
39	Surface/gross	Gross	Gross	Gross	Gross		Positive
40	Surface/microscopic	Surface/microscopic	Microscopic	Microscopic			Positive

ABD: abdominal; LN: pelvic lymph node.

associated with positive peritoneal cytology. Cytology was negative in three patients with microscopic extrauterine disease and one case with gross disease (Table 2). One case had positive peritoneal washing as the only evidence of extrauterine involvement. Overall, the most frequently involved organs were omentum (78%, 14/18 cases), peritoneal fluid (72% 13/18 cases) and ovary (67% 12/18 cases). The ovarian metastasis was mainly in the form of surface involvement (11 of 12 cases). Only one case showed both surface and parenchymal (>0.5 cm tumor nodule involving ovarian parenchyma) tumor deposits. The presence of superficial serous carcinoma involving the endometrium proper appeared correlated with tumor metastasis, as all five of such cases had extrauterine disease at the time of hysterectomy. Nonetheless, even when the tumor was confined to a polyp, 38% (eight of 21 cases) presented with extrauterine disease, including three cases of intraepithelial serous carcinoma.

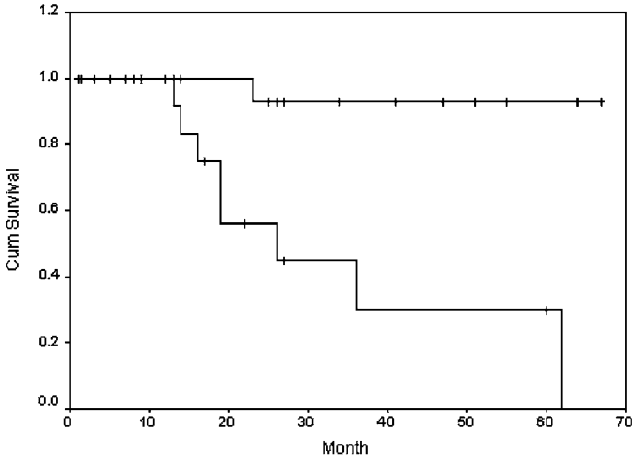

Figure 4 Kaplan–Meier survival curve of two groups of patients with follow-up information. Group 1 ($n=19$): upper curve—patients with tumor confined to their uteri, and group 2 ($n=18$): lower curve—patients with tumor having extrauterine tumor involvement.

Clinical Follow-Up

Clinical follow-up information was available in 37 patients (Table 1) and the overall survival is illustrated in Figure 4, where Kaplan–Meier survival curves were calculated based on the patient's clinical stages. In all, 19 stage I and II patients had follow-ups ranging from 2 to 73 months (median 26 months) with an overall survival rate of 94%. The only patient who died of the disease had a FIGO stage IIA tumor (intraepithelial serous carcinoma involving endocervical mucosa) at presentation. Eight out of 18 patients with stages III and IV disease died of their malignancy. The estimated 5-year survival rate was 24% with a follow-up of 1.5–62 months (median 17 months). One patient with stage IVb disease (Table 1 case 31) survived the disease after 61 months of follow-up without evidence of recurrence. It is noteworthy that the extrauterine disease in this patient was a subcapsular lymph node metastasis consisting of less than 10 neoplastic cells.

Discussion

Recent histological and clinical studies have described a microscopic lesion, referred to as 'EIC', 'endometrial carcinoma *in situ*' or 'uterine surface carcinoma', as an early phase of serous carcinomas.[1–3] Whatever the term used, they essentially

describe an epithelial involvement by the cells of high-grade serous carcinoma. However, in contrast to the usual behavior of conventional carcinoma *in situ* of other organs, patients with 'EIC' may present with extrauterine tumor spread, leading to an advanced stage and a clinical prognosis similar to that of a full-blown serous carcinoma. Three of nine cases of 'EIC' in our study were associated with extrauterine spread and two patients died of the disease. For this reason, it appears inappropriate to consider 'EIC' as an *in situ* neoplasia. Therefore, in this study, we have used the term 'intraepithelial serous carcinoma' to emphasize the unconventional behavior of this lesion. Similarly, Clement and Young[7] have recently indicated that they generally consider 'endometrial intraepithelial carcinoma' as a 'tiny focus' of serous carcinoma, without further qualifying, other than noting its size and location.

Although most of our cases demonstrated a diffuse and strong immunostaining with p53 (score of 7 or above), a percentage of serous carcinomas may harbor a p53 gene alteration that results in a deletion of the gene or an earlier termination of its transcription, and therefore no mutant p53 protein is produced. This may explain a negative result of p53 immunohistochemistry in some of our cases. In practice, we would emphasize and rely on the morphological criteria in making a diagnosis of minimal uterine serous carcinoma, although a positive p53 immunostaining is certainly helpful.

Endometrial polyps are common lesions in women over 40 years of age. They develop as focal, combined hyperplasia of the epithelium, stroma and vessels. The association of an endometrial polyp with serous carcinoma was first reported by Silva and Jenkin[8] to describe 16 patients with superficial serous carcinoma involving an endometrial polyp. In their study, cases with other mixed carcinoma patterns were also included and superficial myometrial invasion was present in one case. Six of these patients had clinical manifestations of extrauterine disease at presentation. They concluded that a serous carcinoma involving an endometrial polyp could represent a multicentric disease, that is, the entire female genital tract and the abdominal peritoneal surfaces being at high risk for concurrent serous carcinoma. Carcangiu described 13 cases of stage IA lesion, of which serous carcinoma was confined to an endometrial polyp in six cases, and involved both a polyp and the endometrium proper in four cases.[4] Wheeler reported that 19 of 21 cases of minimal uterine serous carcinoma involved an endometrial polyp, and in 10 of which the lesion was confined to the polyp.[1] Soslow reported three cases of 'EIC' associated with peritoneal carcinomatosis.[9] In all three, the lesion involved exclusively an endometrial polyp. These studies clearly demonstrated an intimate relationship between a minimal serous carcinoma and an endometrial polyp. However, such a relationship has not been fully investigated and a consideration of an endometrial polyp harboring possible precursor lesions has not been discussed in the literature.

In our series consisting of 40 cases of minimal uterine serous carcinoma, an endometrial polyp was involved by the tumor in 88% of the cases (35 of 40). Corroborating the existing literature, our findings further demonstrate a close topographic relationship between a minimal uterine serous carcinoma and an endometrial polyp. Observed in a couple of cases in this study, the epithelium adjacent to a minimal uterine serous carcinoma displayed mild-to-moderate cytological atypia, but in lesser degree than that of serous carcinoma cells. In one case (Table 1, case 4), the patient presented with a p53 overexpressing intraepithelial serous carcinoma involving an endometrial polyp. She had been diagnosed with an endometrial polyp showing atypical epithelial changes, 13 months prior; however, p53 overexpression was not detected. In a more recent case where multiple endometrial polyps were present (Table 1, case 2), an intraepithelial serous carcinoma was found at the tip of a large endometrial polyp and p53 overexpression was demonstrated in the neoplastic cells. It is worth noting that, in this case, the adjacent glandular epithelium also expressed p53 of similar intensity; however, with only mild-to-moderate cytological atypia (Figure 3). It is conceivable that these epithelial abnormalities may represent early steps of neoplastic transformation leading to a minimal serous carcinoma. As a paradigm in the theory of multistep carcinogensis, most, if not all, invasive colorectal adenocarcinomas arise in a pre-existing adenomatous polyp. All colonic adenomatous polyps develop as a result of epithelial proliferative dysplasia, which may range from mild to so severe as to constitute carcinoma *in situ*. Temporal sequence of mutations in specific genes provide a firm molecular footing in this adenoma-carcinoma sequence for colon cancer,[10] which may have implications in the endometrial carcinogenesis as well.

Overall, 45% (18/40) of minimal uterine serous carcinomas presented with extrauterine tumors in this study. Although multifocal synchronous serous carcinoma is a possibility to explain some of the high-staged cases in our study and others, a clonal, metastatic process is favored. Since endometrial serous carcinomas express a broad spectrum of p53 mutations, the p53 mutation pattern offers a reliable marker for determining clonality of uterine and extrauterine disease.[11] One recent study described three cases of superficial serous carcinoma and one case of 'EIC', all involving an endometrial polyp, but present with clinical stage III disease.[12] In contradiction to the multicentricity theory,[8] the p53 gene mutation profiles of all four minimal serous carcinomas were identical to those of their corresponding extrauterine tumor deposits, consistent with a clonal, metastatic process.[12] Additional molecular clonality analysis of a large number of similar cases, such as ours, is important to reach a conclusion.

Among histological parameters that may predict high-stage tumor presentation, the presence of a superficially invasive component in the endometrium proper appeared significant in our study. This feature was not present in any stage I and II tumors; however, was found in five of 18 cases in which extrauterine metastases were present. Therefore, the presence of this histological finding should alert a pathologist of the likelihood of high-stage disease. It should be emphasized that even an intraepithelial serous carcinoma can present with extrauterine disease.[1] Three such cases in our study had stage IV disease and two of them died.

In November 2001, the Gynecologic Cancers Progress Review Group (PRG) proposed several high-impact priorities concerning gynecologic cancers. Identification of precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indicators and new targets for prevention and treatment were among the number one high-impact priorities. There is a particular concern regarding some high-grade type II endometrial cancers, mainly serous carcinoma, of which there are no defined precursor lesions at the present time, and therefore, the population at risk and effective screening strategies are yet to be identified and developed. Such concern is further exacerbated by the fact that patients with a minimal uterine serous carcinoma without extrauterine spread survived the disease in 94% of the cases in our study, whereas eight of 18 patients with extrauterine tumor spread died of the disease within 5 years. The importance of prevention of spread and confinement of minimal uterine serous carcinoma cannot be overemphasized. Clinically, it is prudent that a complete staging laparotomy is performed, even if the lesion is limited to a polyp. The strong association between a minimal uterine serous carcinoma and an endometrial polyp in postmenopausal women suggests that the latter may provide a microenvironment, within which early neoplastic changes or precursor lesions for serous carcinoma may develop. Such an association deserves a greater attention, both in clinical practice and in exploring the pathogenesis of this highly malignant disease in women.

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