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ORIGINAL ARTICLE

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Endometrial stromal sarcomas: immunohistochemical, electron microscopical and cytogenetic findings in two cases

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Abstract Uterine sarcomas are approximately 3% of all malignant uterine corpus tumours. Of these, the tumours that originate solely in the stromal elements of the uterine wall are infrequent and have not been well characterized cytogenetically. We report two cases of endometrial stromal sarcomas (ESS), one low grade and one high grade, diagnosed by conventional histology, immunocytochemistry, electron microscopy and cytogenetics. Morphologically clear-cut differential structures were seen at optical, immunohistochemical, and electron microscopic levels, permitting a clear differential diagnosis. The low-grade ESS expressed hormonal receptors and vimentin, whereas the high-grade ESS showed no hormone receptors, high Ki-67 activity, and occasional cytokeratin-positive cells. Ultrastructurally, no malignant epithelial differentiation was seen in the tumour cells, but cilia were found in both cases. Cytogenetic study of the low-grade ESS showed pseudodiploid karyotype with chromosomes 6 and 20 rearranged. The high-grade ESS showed a complex karyotype with clonal numerical and structural anomalies. The chromosomes involved in the structural rearrangements were 1, 3, 6, 7, 13, 14, 15, 17, 19, and 21.

Key words Endometrial stromal sarcoma · Cytogenetics · Chromosomes

Introduction

Uterine sarcomas are uncommon neoplasms, accounting for 2–4% of all uterine malignant tumours. These sarcomas can be divided into three groups: leiomyosarcomas, endometrial stromal sarcomas (ESSs), and malignant mixed mesodermal tumours [24]. Approximately 26% of all uterine sarcomas are endometrial stromal sarcomas. These tumours are pure homologous sarcomas that can be classified into two distinct entities based primarily on mitotic count: low-grade (LG-ESS) and high-grade tumours (HG-ESS) [1]. Histology, immunohistochemistry and electron microscopy of these tumours are well documented [1, 3, 7], but reports of cytogenetic findings in endometrial stromal sarcomas are few, only 11 ESSs having been reported (10 LG-ESSs and 1 HG-ESS) [4, 5, 9, 10, 13–15, 21, 23]. Rearrangements of chromosomes 6, 7 and 17 are the most consistent features. Translocation between chromosomes 7 and 17 seems to be typical of a group of low grade ESSs. We describe the morphological and cytogenetic studies in two new cases, one LG-ESS and one HG-ESS, correlating the immunohistochemical and electron microscopical findings with the chromosomal rearrangements.

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Case report

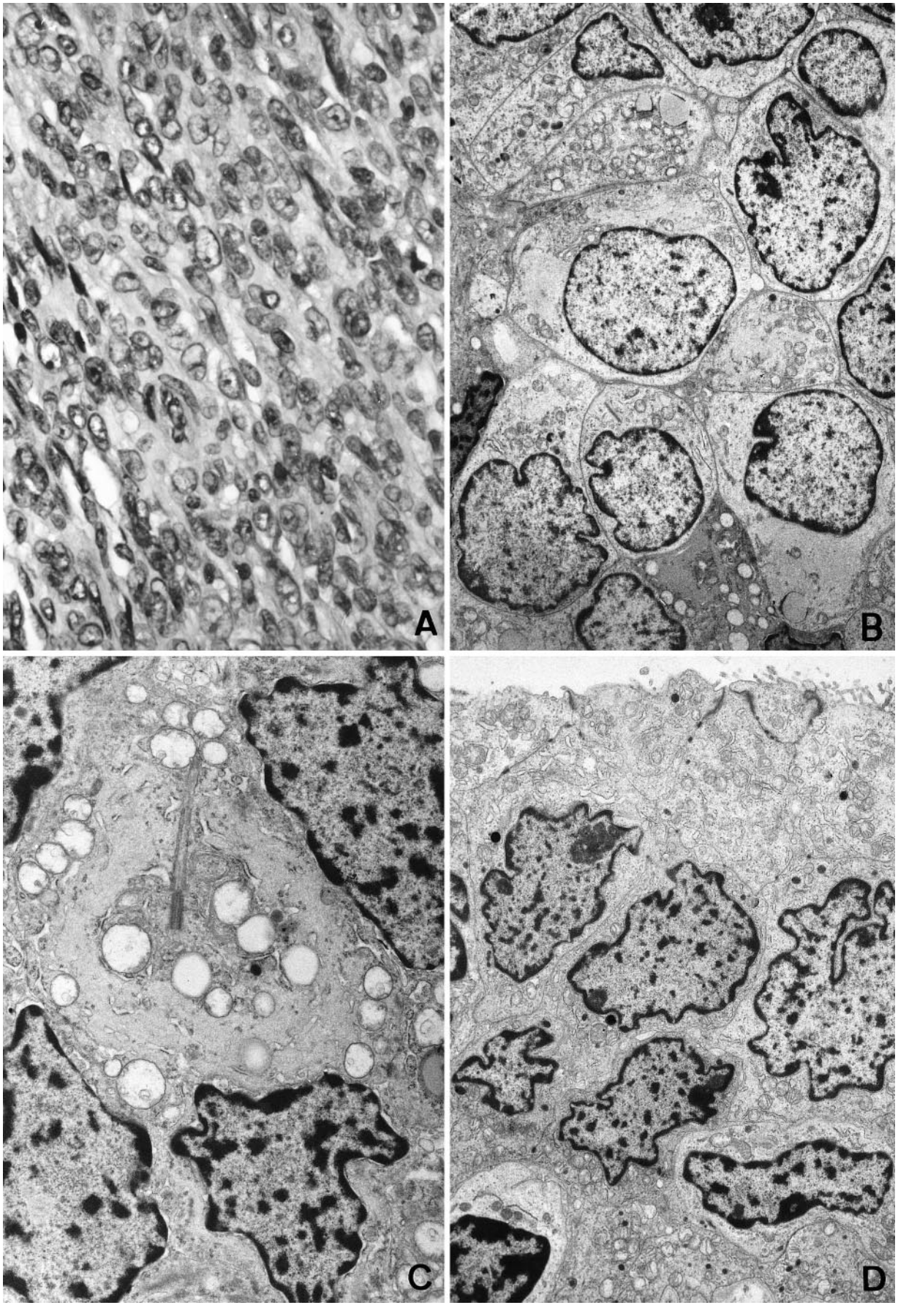
Clinical data

Case 1

A 52-year-old woman without antecedents of interest presented with abnormal bleeding and menstrual irregularities 3 years before her admission. Ultrasound examination revealed an increase of the endometrial line. Colposcopy and cytology were negative, and with the clinical diagnosis of endometrial polyp, a curettage biopsy was performed, followed by hysterectomy and bilateral ovariectomy. There was no evidence of spread. Currently, the patient is alive and free of disease.

Case 2

A 71-year-old woman who had been menopausal from the age of 54 presented with spotting and metrorrhagia 10 days previously. Colposcopy and cytology were negative, and with the diagnosis of postmenopausal metrorrhagia a curettage biopsy was performed. After diagnosis the patient underwent bilateral ovariectomy and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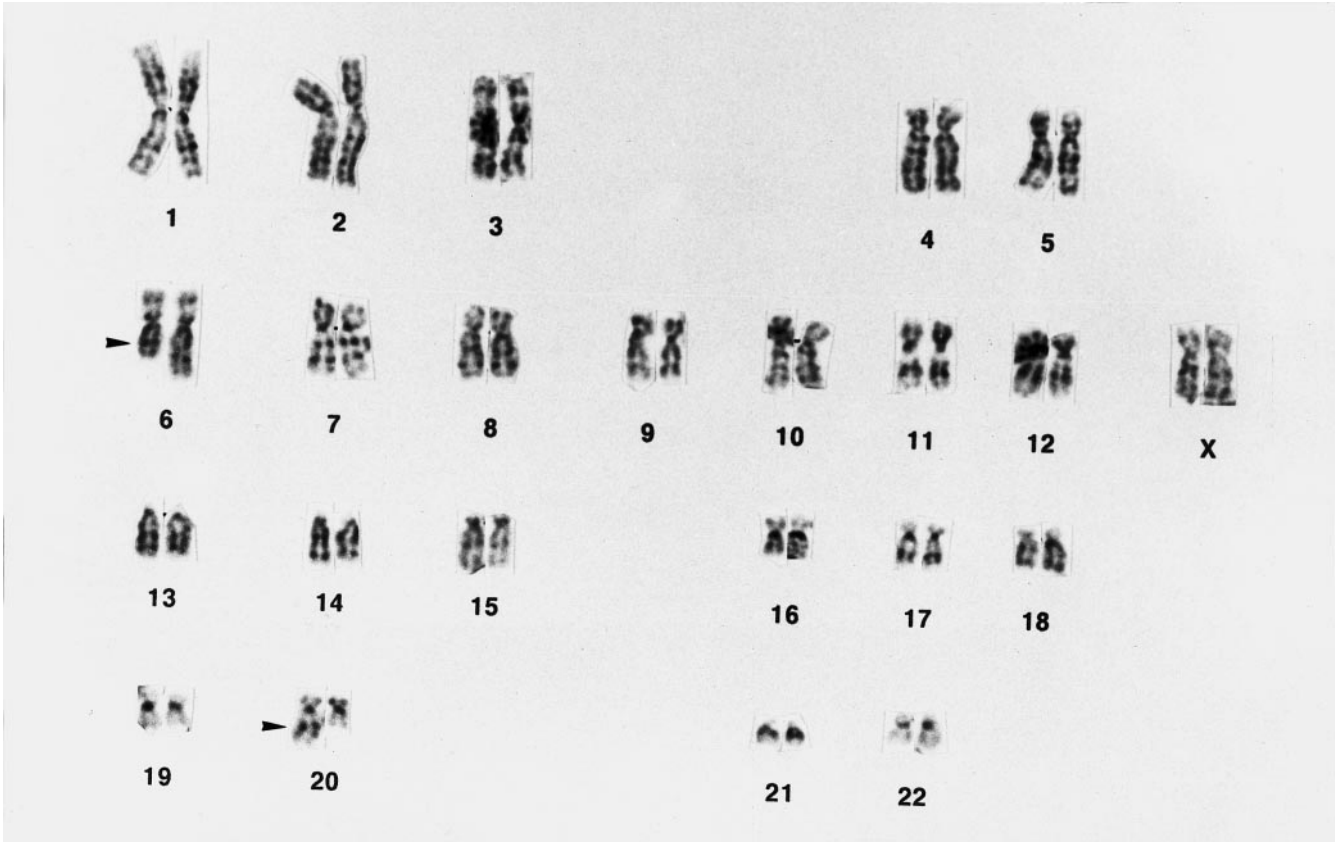


Fig. 2 G-banded karyotype of case 1. *Arrows* indicate the del(6)(q22) and add(20)(q13)

partial hysterectomy followed by radiotherapy (45, 6 Gy). One month later, progression of disease and multiple lung metastases led to respiratory failure and the patient died. No autopsy was performed.

Materials and methods

For light microscopy, material from curettage and surgical specimens was fixed in 10% formaldehyde and embedded in paraffin. Slides 4 µm thick were stained with haematoxylin and eosin. For immunohistochemistry, paraffin sections were analysed following the ABC peroxidase method, with the following antibodies: vimentin (Dako 1:50), smooth muscle actin (Biogenex 1:50), desmin (Dako 1:100), myogenin (Santa Cruz Biotech 1/100), S-100 (Dako 1:300), neuron-specific enolase (Biogenex 1:100), EMA (Dako 1:100), Ki 67 (Immnunogenetics 1:50), cytokeratin AE1-AE3 (Concepta 1:50), oestrogen and progesterone receptors (Novocastra prediluted).

For transmission electron microscopy, tissue was fixed in gluteraldehyde, postfixed in 1% osmium tetroxide, dehydrated in graded alcohols, and embedded in Epon. The samples were cut into 1 µm-thick sections and stained with toluidine blue for selection, by optical microscopy, of representative fields of the tumour. Ultrathin sections were examined using a Jeol 100B microscope (Tokyo).

Chromosome analysis was performed on tumour biopsies obtained from the primary tumours. For culture, fragments of sterile tumour tissue were dissociated enzymatically using RPMI 1640 medium containing 0.02% collagenase type II and incubated at 37°C for approximately 20 min. Cell suspension was seeded into 25-cm^2 tissue culture Falcon flasks containing RPMI 1640 medium and antibiotics supplemented with 20% fetal bovine serum and were incubated at 37° C in a 5% CO_2 atmosphere. When cultures entered exponential growth, they were harvested after Colcemid (0.02 µg/ml) treatment. Slides were prepared by the conventional technique. Air-dried slides were banded by trypsin-Giemsa. Standard International System of Human Cytogenetic Nomenclature (ISCN) was used to describe chromosomal abnormalities [18].

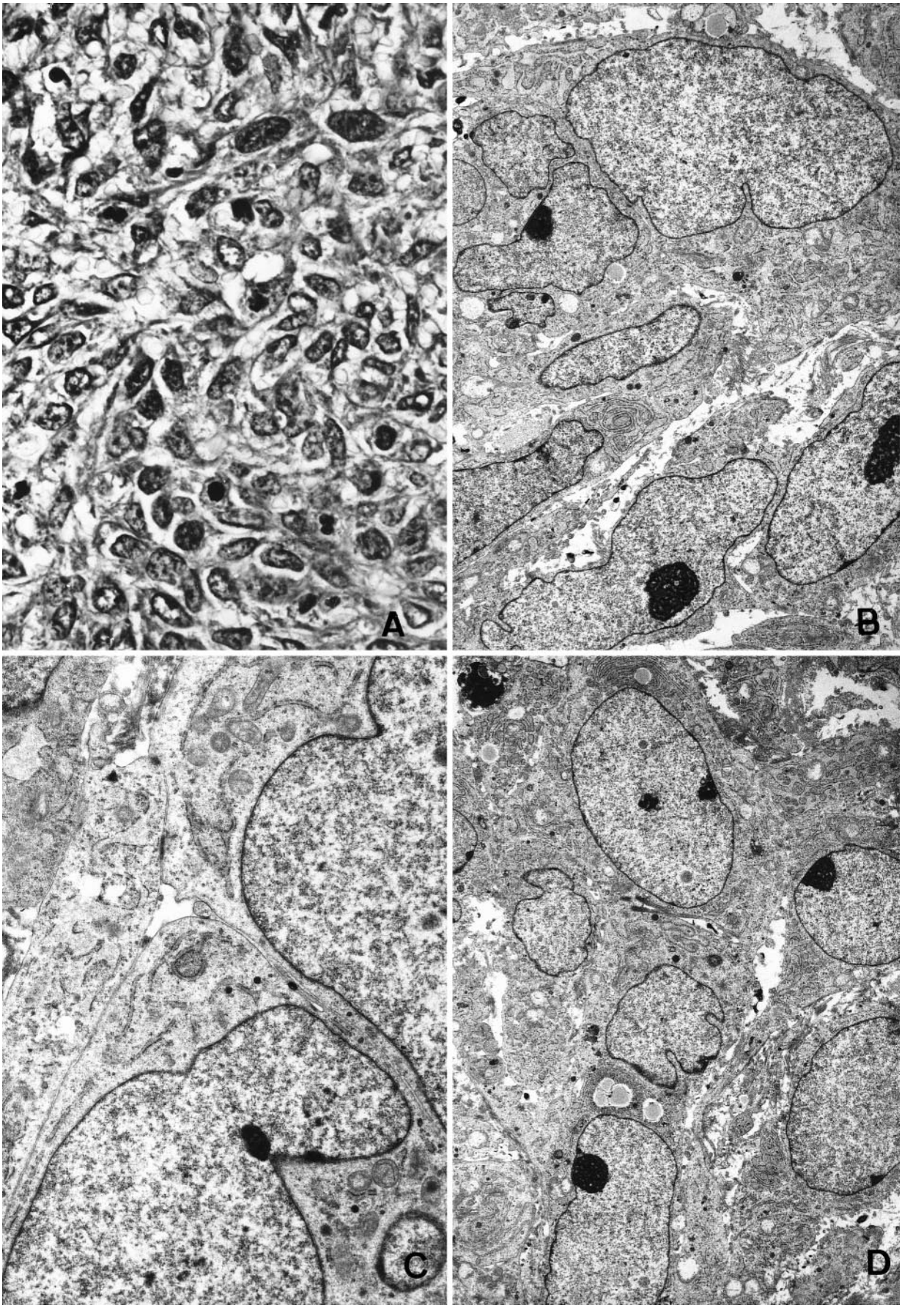
◀ **Fig. 1A–D** Case 1. **A** Histology of the LG-ESS showing cells arranged in fascicles. HE, ×40. **B** Electron micrographs of representative fields of the tumour. Round nuclei with dispersed chromatin, surrounded by cytoplasm containing few organelles. ×13,000 **C** Presence of intracytoplasmic cilium and bundles of microfilaments ×32,000 **D** Uterine gland structures showing cell-to-cell attachments. ×17,000

Results

Case 1

Grossly, several white fragments were obtained by curettage. After diagnosis, hysterectomy revealed a polypoid mass 3 cm in diameter filling the endometrial cavity and apparently invading the inner third of the myometrium.

Microscopically, cells configurating the tumour resembled normal proliferative endometrial stroma. They were arranged in fascicles or solid nests. The cells were uniform in size, tightly packed, with a round or elongated contour configurating a spindle shape with oval nuclei containing dispersed chromatin and inconspicuous nucleoli (Fig. 1A). Tumour necrosis was rare and no nuclear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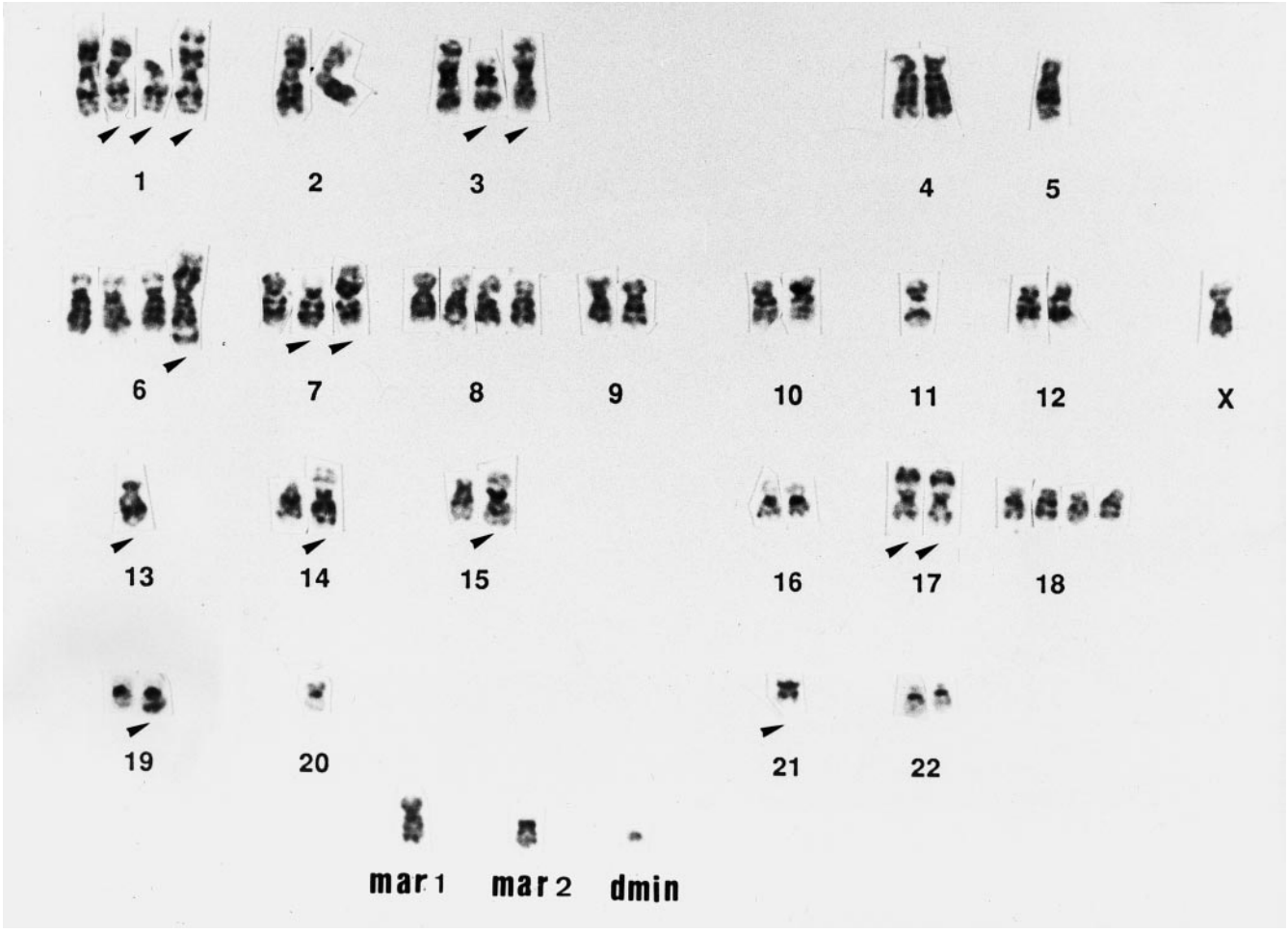

Fig. 4 G-banded karyotype of tumour cells of case 2. *Arrows* point to the structural anomalies of chromosomes 1, 3, 6, 7, 13, 14, 15, 17, 19, and 21

atypia was seen. We counted less than 2 mitoses/10 HPF. There was a prominent vascular component consisting mostly of capillaries. Isolated endometrial glands were included within the tumour cells, with an atrophic configuration. No atypia or functional activity was seen.

At the immunohistochemical level, both oestrogen and progesterone receptors appeared strongly positive in nearly 80% of the cell nuclei. Ki-67 was positive in about 5% of the cells. The cytoplasm showed intense vimentin positivity, but epithelial markers (EMA, EA1, EA3, CAM 5.2) were seen only in isolated glands engulfed by the tumour cells. No neural or muscle cell markers were detected in the tumour (negativity for S-100, neurofilaments, actin, and desmin).

◀ **Fig. 3A–D** Case 2. **A** Histology of the HG-ESS tumour showing spindle-shaped and pleomorphic multinucleated cells. HE, ×40. **B** Multinucleated giant cells and sarcomatous cells with oval nuclei containing finely dispersed chromatin and large nucleolus. ×14,000. **C** Tight junctions between two tumour cells ×28,000 **D** Cells appear to be of mesenchymal origin, with presence of cilia extending through the plasma membrane. ×12,000

Ultrastructurally, the cells were closely packed, round or elongated with short cell projections and homogeneous appearance (Fig. 1B). Large cell contacts and tight junctions were found linking neighboring cytoplasms. Occasional cilia were observed (Fig. 1C). Nuclei were round, oval, and large, filling most of the cell body but surrounded by a cytoplasmic rim. A chromatin pattern with condensed nuclear bodies at the peripheral border of the nuclear membrane was predominant. Nucleoli were scarce and small. Interstitial spaces were filled by capillaries and occasional collagen bundles. The epithelial component (non-transformed glandular structures) were easily distinguished, based upon the presence of basal lamina, more abundant cytoplasm with secretory granules, microvilli and cell-to-cell attachments of complex type with numerous cell junctions (Fig. 1D). Keratin filaments were seen.

Twenty-five metaphases were analysed. The tumour cells were pseudodiploid and showed monoclonal abnormalities, resulting in the following karyotype: 46,XX,del(6)(q22),add(20)(q13) (Fig. 2).

Case 2

Microscopically, a highly malignant mesenchymal neoplasm with a diffuse growth pattern was found in all the

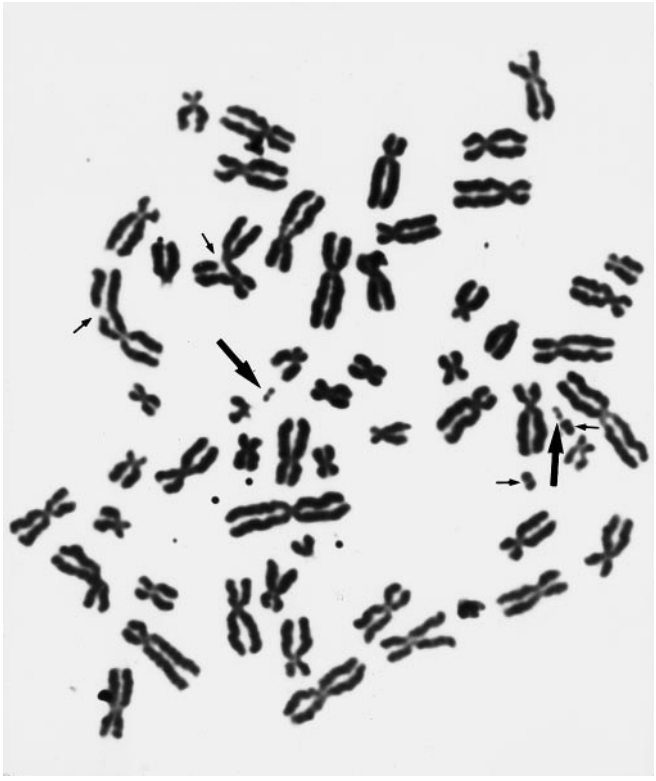

Fig. 5 Partial metaphase of case 2. *Arrows* indicate double minutes, breaks and acentric fragments

material provided for microscopy (Fig. 3A). Most of the specimens were necrotic or haemorrhagic. No epithelial differentiation was observed, and the tumour cells infiltrated the myometrium, separating normal muscle fascicles. The cells were predominantly spindle shaped, but numerous pleomorphic multinucleated cells were also found. Nuclear atypia was remarkable, and there was a high mitotic count (10–15 mitoses/10 HPF). Vessels with dilated lumens and irregular contours were frequently seen. No muscle or osteogenic cell differentiation was detected.

At the immunohistochemical level, tumour cells did not express oestrogen or progesterone receptors, but the Ki 67 staining was positive in nearly 50% of the nuclei. Vimentin was strongly positive in all cell cytoplasms but no neural or muscle cell filaments were seen. Isolated cells (approximately 1–2 in 100) expressed cytokeratin (CAM 5.2, AE1, AE3) but not EMA. This positivity was strong and limited exclusively to the cytoplasm.

Ultrastructurally, this sarcoma was extremely pleomorphic with various cell types of mesenchymal appearance, mainly elongated, polyhedric or round in contour. Cell projections and cytoplasmic protrusions appeared. Nuclei, one or several per cell, were pleomorphic with irregular contours and finely dispersed chromatin (Fig. 3B). The nucleoli were extremely prominent. The cytoplasm showed an abundant RER component, numerous mitochondria and bundles of filaments. Presence of activated lysosomes and phagocytic bodies were seen together with apoptotic cells. Interstices were filled by collagen bundles and focal membrane-like material was adhering to the cell membrane. Tight junctions or small desmosomes were found, as well as large areas of membrane adhesion (Fig. 3C). Occasionally we saw cilia emerging from one such undifferentiated mesenchymatous element (Fig. 3D).

Twenty-three metaphases were analysed. The chromosomal number ranged from 49 to 78, with a mode of 54. The chromosome analysis revealed a complex karyotype:

53–55,X,–X,del(1)(p32),+del(1)(p21),+der(1)t(1;3)(p32;p21),del(3)(p21),+der(3)t(3;15)(q10;q10),–5,+6,+der (6)add (6)(p11)add(6)(q27), add(7)(p11),+add(7)(p21),+8,+8,–11,–13,der(13;21)(q10;q10),add(14)(p11),der (15)t(6;15)(p21;p12),der(17)t(3;17)(p21;p13)x2,+18,+18,add(19)(q13),–20,der(21;21)(q10;q10),+mar1,+mar2,+dmin (Fig. 4).

Some metaphases showed chromosomal breaks, double minutes, triradial figures and acentric fragments (Fig. 5).

Discussion

Uterine sarcomas are a heterogeneous group of neoplasms, representing 2–4% of all malignancies of the uterus [24]. Those that consist exclusively of malignant mesenchymal tissues are considered to be pure sarcomas, which are subdivided into two grades: LG-ESS and HG-ESS. In the past, morphology and mitotic activity were the only variables that could distinguish between low- and high-grade endometrial stromal sarcomas. The term “low-grade endometrial stromal sarcoma” is used for neoplasms made up of cells that resemble stromal cells of the proliferative-phase endometrium, whereas a “high-grade endometrial stromal sarcoma” is made up of cells that are more atypical but still resemble endometrial stromal cells. In the HG-ESS presented here cytokeratin reactivity was expressed in isolated tumour cells, but not the epithelial membrane antigen. A biphasic histological pattern with apparent epithelial differentiation has been observed in the various subtypes of endometrial stromal neoplasm [7, 16]. While the cytokeratin reactivity may signify epithelial differentiation in most instances, it is less well known that cytokeratin may be found in normal smooth muscle, myometrium and smooth muscle tumours [20]. Indeed, three of six (50%) ESSs stained positive for keratin in a review of 9 cases [2]. Moreover, electron microscopy provides further clues for the diagnosis of these tumours, both of which displayed mesenchymal differentiation with abundant intermediate filaments of vimentin type. The ultrastructural features of the LG-ESS are similar to those of stromal cells in an early to midproliferative phase, with an undifferentiated appearance and few cytoplasmic organelles. The pleomorphism and cytological atypia seen in HG-ESS (case 2) by light microscopy also was observed at the ultra-

Table 1 Summary of cytogenetic data on endometrial stromal sarcomas reported in the literature.

Case	Histological Type	Karyotype	Ref.
1	LG-ESS	45,XX,-10,der(19)ins(10;19)(p11;p13q13)/45,idem,del(1) (p21or22) /45, idem,del(1)(p21.1p35)	[4]
2	LG-ESS	46,XX,t(7;13)(q11.1;p13),t(7;17)(p21;q12),del(11)(q13q21)	[23]
3	LG-ESS	46,XX,del(5)(q31.1),der(7)t(6;7)(p21;p22)/46,XX	[9]
4	LG-ESS	46,XX,t(7;17)(p15–21;q12–21) /46,idem,-7,+der(?)t(?;7)(?;q11)/45,idem, -7,dic(15;22)(p11;p11),+der(?)t(?;7)(?;q11)/46,XX	[5]
5	LG-ESS	49,XX,+7,+8,+9,der(14)t(14;22)(p13;q12)	[15]
6	LG-ESS	46,XX,del(5)(q33),-7,+der(7)t(6;7)(p21;p21)	[15]
7	HG-ESS	80,XX,i(1p),del(1)(p11),del(6)(q12),del(12)(p11),der(16)t(16;?)(q12;?),der(19) t(19;?)(q13;?)	[15]
8	LG-ESS	46,XX,der(3)t(3;7)(p12;p12),der(6)t(3;6)(6;7)(p13;p21q13;p21),der(7)t(6;7)(7;6) q13;p13q21;p21),inv(17)/46,XX,inv(17)(p12q11)	[14]
9	ESS	47,XX,der(3)t(3;6)(q29;p21.1),der(6)t(3;6)(q21;q27),+19	[10]
10	LG-ESS	46,XX,der(6)t(6;11)(p21;q21),del(6)(q15),add(7)(p21),t(7;17)(p15–21;q12–21),+9,-11	[21]
11	LG-ESS	46,XX,t(7;17)(p14~21;q11.2~21),der(7)t(7;16)(p14~15;q22)t(7;9)(q22;q22),der(9) t(7;9)(q22;q22),del(16)(q22)/47,idem,del(3) (p13p23),+mar/46,XX	[13]
12	LG-ESS	46,XX,del(6)(q22),add(20)(q13) [18]	Present case 1
13	HG-ESS	53–55,X,-X,del(1)(p32),+del(1)(p21),+der(1)t(1;3)(p32;p21),del(3)(p21),+der(3) t(3;15)(q10;q10),-5,+6,+der(6)add(6)(p11)add(6)(q27),add(7)(p11),+add(7)(p21), +8,+8,-11,-13,der(13;21)(q10;q10),add(14)(p11),der(15)t(6;15)(p21;p12),der(17) t(3;17)(p21;p13)x2,+18,+18,add(19)(q13),-20,der(21;21)(q10q10),+mar1, +mar2,+dmin [23]	Present case 2

structural level. Immature appearing nuclei, which occasionally multiple or bizzarely shaped nuclei surrounded by cytoplasm, were present. The presence of cilia has been reported in numerous mesenchymal tumours [3].

Cytogenetic studies of ESSs are few, even including the present two cases. Thirteen cytogenetically investigated ESS have been reported, 11 of which were LG-ESS and 2 were HG-ESS (Table 1). Of the 11 cytogenetically studied LG-ESS, including case 1 of the present study, 8 were pseudodiploid and 3 near-diploid, while 1 of the HG-ESSs tumours was hypertriploid [15] and 1, hyperdiploid (case 2 of the present study). These results are consistent with previous studies of ploidy in ESS; low-grade sarcomas have shown DNA indices approximating a diploid DNA content, whereas higher grade sarcomas generally show an aneuploid population with DNA content between triploid and tetraploid [6, 19]. In the HG-ESS presented here, the chromosomes that were overrepresented were: 1q, 3p, 6, 7, 8, 15, 18, and 21. Losses of chromosomes X, 5, 11, 13, and 20 were observed. It is not clear what the significance of these chromosomal losses is; they may be involved in ESS tumourigenesis or may represent loss of tumour suppressor genes, a fact that is difficult to determine owing to the limited number of cases studied cytogenetically.

All ESSs show clonal structural abnormalities. Rearrangements of chromosomes 6, 7 and 17 are the most consistent features. In our cases clonal abnormalities of chromosome 6 were present in both, a deletion of chromosome 6 at q22 band in case 1, and a rearranged chromosome 6 with material of unknown origin transferred to p11 and q27 bands, and a der(15)t(6;15)(p21;p12) in case 2. Deletions of chromosome 6 have been described at different breakpoints [15, 21]. Rearrangements of chromosome 6 with different chromosomes affecting p21 band have also been seen in 5 cases of LG-ESS [9, 10, 14, 15, 21]. Moreover, an identical chromosome site was involved in the mesenchymal component of an endometrial polyp [8].

In case 2, chromosomes 7 and 17 were involved with different structural rearrangements, but t(7;17) was not present. This translocation seems to be a primary specific cytogenetic abnormality in a group of LG-ESSs, but was not seen in HG-ESS.

Two cases of HG-ESS were characterized cytogenetically (case 7 of Table 1 and case 2 of the present study), presenting deletion of 1p, add 19 at q13 and dmin as common chromosomal anomalies. Del 1p was also seen in a case of LG-ESS [4] and is common in malignant mixed mesodermal tumours (MMMT) of the uterus [11], as well as in many other tumour types [17], supporting the hypothesis that a suppressor gene whose loss or inactivation could be a common event in the progression of many solid tumours may be located here [12]. Chromosome 19 at q13 band is often involved in MMMT of the uterus [11], arising mostly through the addition of material of unknown origin to 19q13. Aberrations of chromosome 19 have already been demonstrated in other LG-ESS, even if the chromosomal change was different [4]. Whether there is any relationship between cytogenetic aberrations in ESS and MMMT remains speculative. Double minutes were observed in both cases of HG-ESS,

but have not been seen in LG-ESS. This finding may indicate oncogene amplifications, which are frequently associated with more aggressive forms of human cancer and which may contribute to tumour progression [22]. The breaks, triradial figures and acentric fragments observed in this case of HG-ESS represent cytological markers of genomic instability.

Based upon these two cases of ESS we infer that the low-grade stromal sarcomas have relatively simple karyotypes with rearrangements, generally of two or three chromosomes, in contrast to the multiple numerical and structural aberrations seen in HG-ESS tumours.

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