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Supernumerary ring chromosomes and nuclear blebs in some low-grade malignant soft tissue tumours: atypical lipomatous tumours and dermatofibrosarcoma protuberans

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Abstract We investigated the diagnostic significance of supernumerary ring chromosomes in low-grade soft-tissue neoplasms. Chromosome slides were prepared from 123 samples of soft-tissue tumours using the standard trypsin-Giemsa banding technique. Supernumerary ring chromosomes were found in 6 cases of soft tissue tumours: 5 cases of atypical lipomatous tumour (ALT) and 1 case of dermatofibrosarcoma protuberans (DFSP). By chromosome painting with fluorescence in situ hybridization (FISH), the ring chromosome in 1 ALT was painted over its entire length with the chromosome 12 probe. Nuclear blebs and micronuclei, which were observed in each case of ALT, also contained chromosome 12 material; and these structures may represent a topological distribution of ring or giant marker chromosomes in the interphase nuclei. Our findings suggest that supernumerary ring chromosomes are characteristic of some low-grade soft tissue neoplasms including ALT and DFSP.

Key words Atypical lipomatous tumour · Liposarcoma · Atypical lipoma · Dermatofibrosarcoma protuberans · Low-grade soft tissue neoplasm · Supernumerary ring chromosome

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Introduction

Malignant soft-tissue tumours often show clonal chromosomal aberrations, many of which are specific for particular tumour types [4, 11, 14, 22, 23, 30, 33, 37]. Recent karyotypic and morphological studies in the United States and Europe have demonstrated that some low-grade malignant neoplasms, including atypical lipomatous tumours (ALT: atypical lipoma and well-differentiated liposarcoma) [3, 7, 9, 16, 28, 29, 34–36], dermatofibrosarcoma protuberans (DFSP) [17, 20, 21, 24–27, 31] and parosteal osteosarcoma [19, 24, 32] are characterized by supernumerary ring or giant marker chromosomes as the sole consistent abnormality.

However, the relationship between the supernumerary ring chromosomes and the different subtypes of well-differentiated liposarcoma (lipoma-like, sclerosing, or inflammatory) and the detailed histological features in these ring-positive tumours have yet to be documented. In particular, the diagnostic significance of these chromosomal abnormalities in the inflammatory type of liposarcoma still needs to be demonstrated, since this type of ALT often presents with worrying histological features that can easily be confused with either a lipoma or a lipogranulomatous lesion or a primary lymphoproliferative process [1, 5, 13].

We therefore investigated the occurrence of supernumerary ring or giant marker chromosomes in the soft-tissue tumours in an attempt to clarify the relationship between these karyotypic abnormalities and low-grade malignant neoplasms. The present study is the first report from the Asian region regarding the presence of ring and giant markers in low-grade soft-tissue tumours.

Materials and methods

Fresh surgical materials from 185 soft tissue tumours were examined for cytogenetic analysis at the Department of Pathology, Fukuoka University School of Medicine from 1986 to 1996. Meta-

Table 1 Clinicopathological features and karyotypes in six cases of low-grade soft-tissue neoplasms (*F* female, *M* male, *Lt* left, Rt right, *AIML* atypical intramuscular lipoma, *WDL* well differentiated liposarcoma, *DFSP* dermatofibrosarcoma protuberans, *cp* composite karyotype, *ANED* alive with no evidence of disease, *AWR* alive with recurrence, *NA* not available)

Case no.	Age (years)	Sex	Site	Histological type	Karyotype	Follow-up
1	53	F	Lt. thigh	AIML	47, XX, +r[a]	ANED, 3 months
2	58	F	Rt. thigh	WDLS, lipoma-like	47, XX, +r	ANED, 5 years
3	69	M	Rt. thigh	WDLS, lipoma-like	47–50, XY, +1–3r [cp12]	NA
4	48	F	Retroperitoneum	WDLS, sclerosing	45–49, XX, +r1,+r2+m [cp32]	AWR, 3 years 4 months
5	56	M	Rt. thigh	WDLS, inflammatory	47, XY, +r [3] / 48, XY, +7, -8, del(9)(p21p22),+2r [3]	ANED, 1 year
6	43	F	Back	DFSP	47, XX, +r	ANED, 3 years 4 months

[a] A giant marker chromosome was found to be a nonclonal abnormality in case 1

phase preparations were obtained from 123 of these samples. There were 35 cases of lipogenic tumours including 5 cases of ALT (atypical lipoma, 1; well-differentiated liposarcoma, 4), 18 cases of myxoid liposarcoma, 2 cases of round cell liposarcoma, 4 cases of pleomorphic liposarcomas, and 6 cases of benign lipomatous tumour (ordinary lipoma, 3; intramuscular lipoma, 1; angiolipoma, 1; lipoblastoma, 1). In addition, 1 case of DFSP was found among the samples examined.

For light microscopy, the surgically removed tumours were fixed in 10% formalin for 24 h at room temperature and then embedded in paraffin; thereafter 4-μm-thick sections were stained with haematoxylin and eosin.

Chromosome slides were prepared from the short-term cultured tumour cells by the standard trypsin-Giemsa banding technique [22, 23]. The karyotypes were described on the basis of the short system of the International System for Human Cytogenetic Nomenclature [10]. In each ALT, the rest of the cell suspension was analysed for fluorescence in situ hybridization (FISH; chromosome painting), by using a digoxigenin-labelled total chromosome 12 probe (COATASOME 12, Oncor, Gaithersburg, Md.), as described elsewhere [11]. The chromosome preparations were denatured at 75°C for 3 min, while the probe was denatured at 75°C for 10 min. Hybridization at 37°C was done overnight. The hybridization signal was detected using rhodamine-labelled anti-digoxigenin Fab fragment (Boehringer Mannheim, Mannheim, Germany). The slides were counterstained with 0.5 μg/ml 4'-6-diamidino-2-phenylindole (DAPI, Sigma, St Louis, Mo.) and visualized with a Zeiss Axioskop fluorescence microscope and an in situ imaging system (isis, Carl Zeiss Vision, Oberkochen Germany).

Results

The clinical features of 6 patients with ring chromosomes are summarized in Table 1. All 5 ALTs occurred as a deep-seated soft-tissue mass in adult Japanese patients over 40 years old; there were 2 men and 3 women. Four ALTs involved the skeletal muscles of the thigh, while the other 1 was located in the retroperitoneum. The patient with retroperitoneal ALT had two recurrences but was still alive with disease 3 years after the first excision. DFSP developed as an elevated nodular lesion in the back of a 43-year-old female. All patients were treated by wide local excision, except for the 1 with retroperitoneal ALT, for whom radical surgery was judged to be impossible.

Macroscopically, each ALT presented as a lipoma-like lobulated mass ranging from 4 to 20 cm in size. The tumours were generally well delineated but often had a partially infiltrative border to the adjacent skeletal muscle. The cut surface varied from yellow to yellowish white, with irregular areas of fibrous tissue and/or slight myxoid changes.

Microscopically, the ALT in case 1 showed features of intramuscular lipoma with minimal atypia, invading the deep musculature of the thigh. Although the neoplasm was composed almost entirely of mature fat cells, there were considerable variations in the size and shape of the fat cells (Fig. 1a). Only after a close examination of multiple sections from the tumour were a few atypical cells detected (Fig. 1b).

The other 4 cases of ALT represented examples of well-differentiated liposarcoma including 2 lipoma-like (cases 2 and 3), 1 sclerosing (case 4) and 1 inflammatory (case 5) type tumour. The lipoma-like well-differentiated liposarcoma closely resembled a lipoma except for the presence of occasional lipoblasts and broad fibrous septa containing atypical cells with hyperchromatic nuclei (Fig. 2). The sclerosing type liposarcoma (case 4) consisted of irregular clusters of atypical lipoblasts and fat cells, embedded in a dense fibrous areas with a meshwork of collagen fibres (Fig. 3). Many lipoblasts exhibited spider-web features, characterized by a multivacuolated cytoplasm and scalloped or indented nuclei. Some nuclei-containing pseudoinclusions or vacuoles (Lochkern) were also found among the tumour cells.

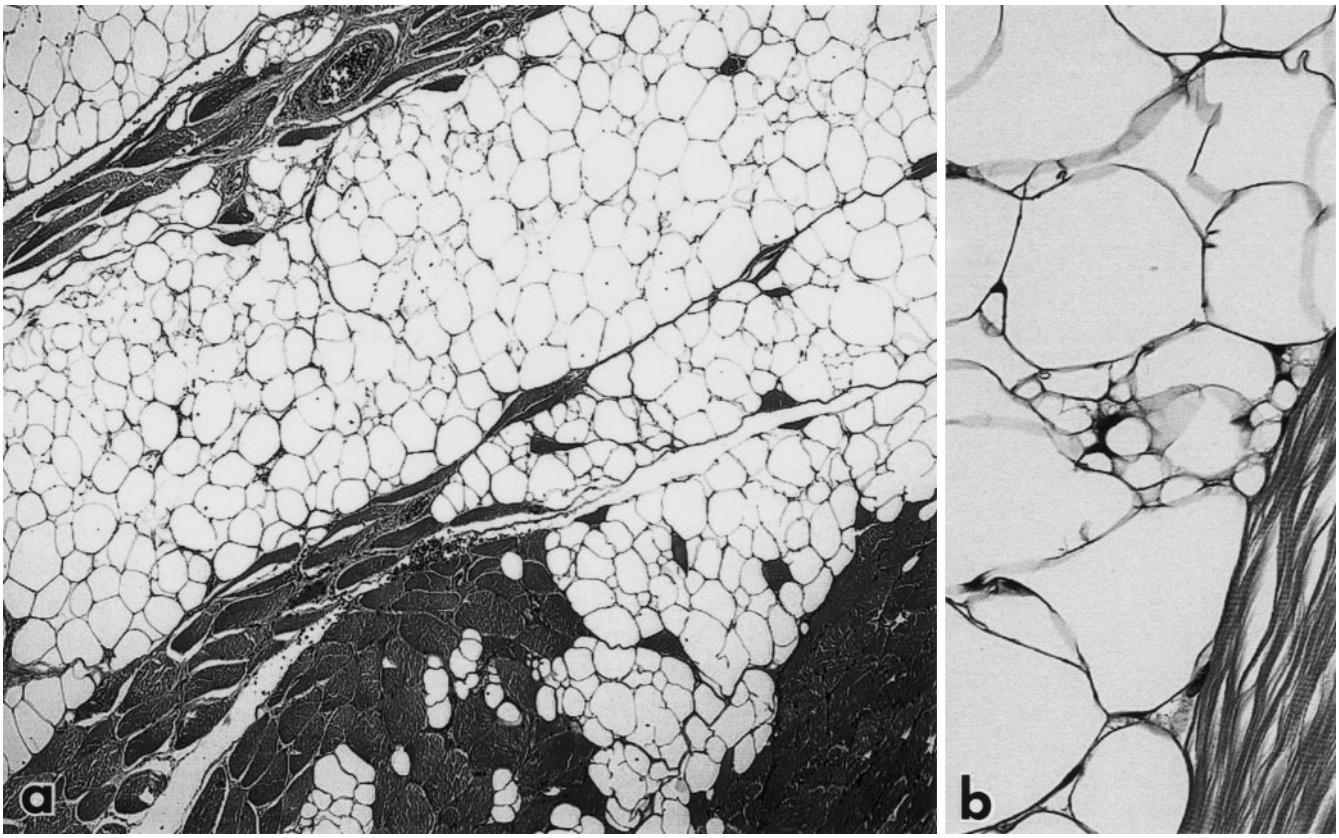

Fig. 1 **a** An atypical intramuscular lipoma (case 1) invading the deep musculature of the thigh. Although the neoplasm is composed almost entirely of mature fat cells, there are considerable variations in the size and shape of fat cells. Haematoxylin and eosin, ×72 **b** Some atypical cells possessing a hyperchromatic nucleus and multivacuolated cytoplasm. Haematoxylin and eosin, ×360

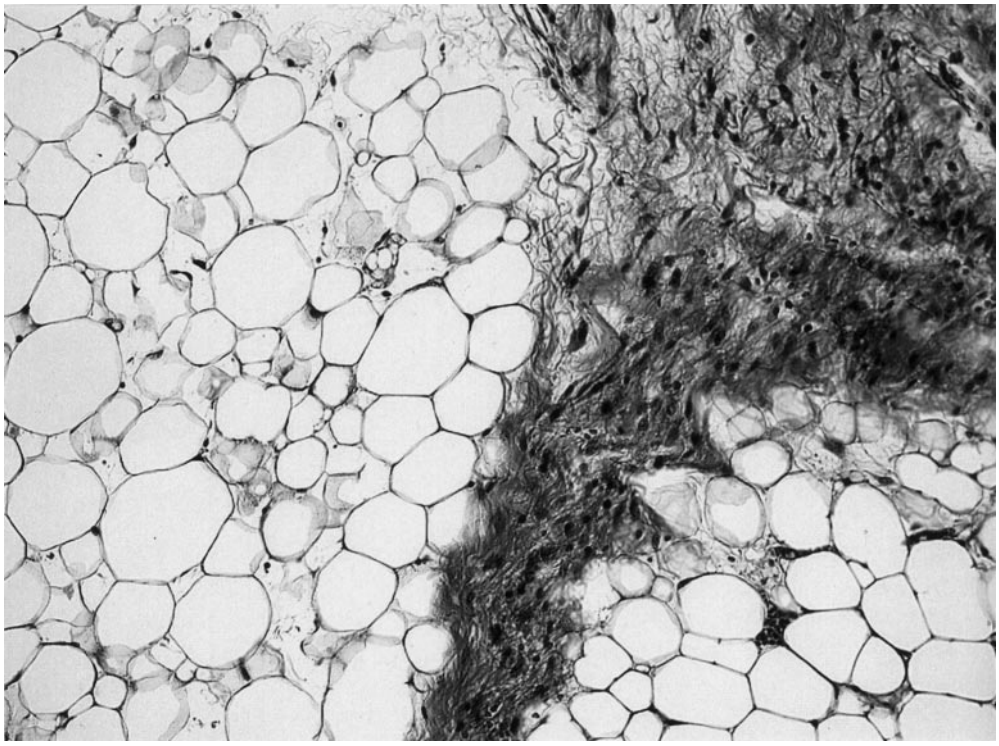

Fig. 2 A lipoma-like type of well-differentiated liposarcoma (case 2). Lobules of fat cells are divided by thick fibrous septa containing atypical cells with hyperchromatic nuclei. Haematoxylin and eosin, ×180

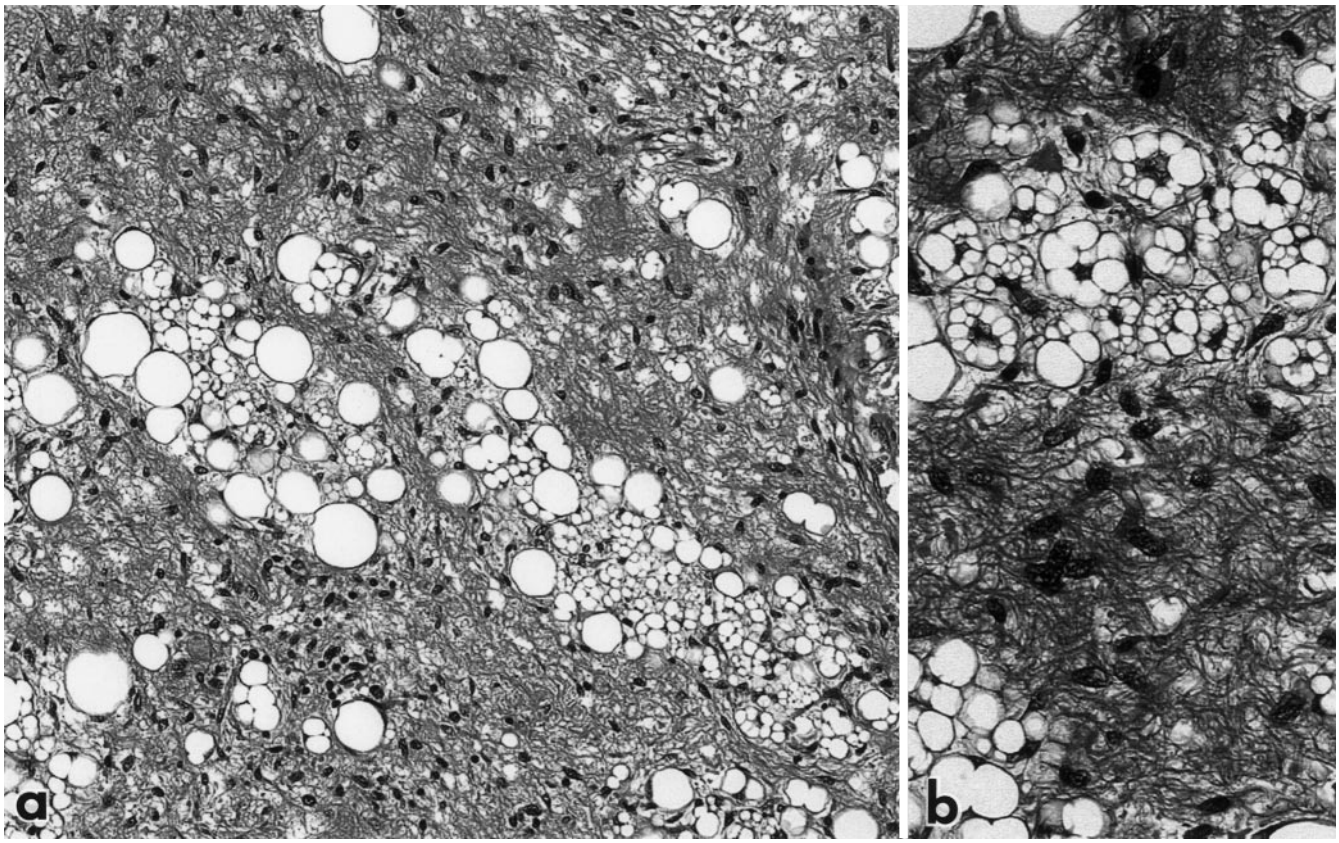

Fig. 3 **a** A sclerosing type liposarcoma (case 4) consisting of irregular clusters of atypical lipoblasts and fat cells embedded in an abundant fibrous matrix with a meshwork of collagen fibres. ×120 **b** Many lipoblasts exhibit spiders' web features, being characterized by multivacuolated cytoplasm and scalloped or indented nuclei. Haematoxylin and eosin, ×360

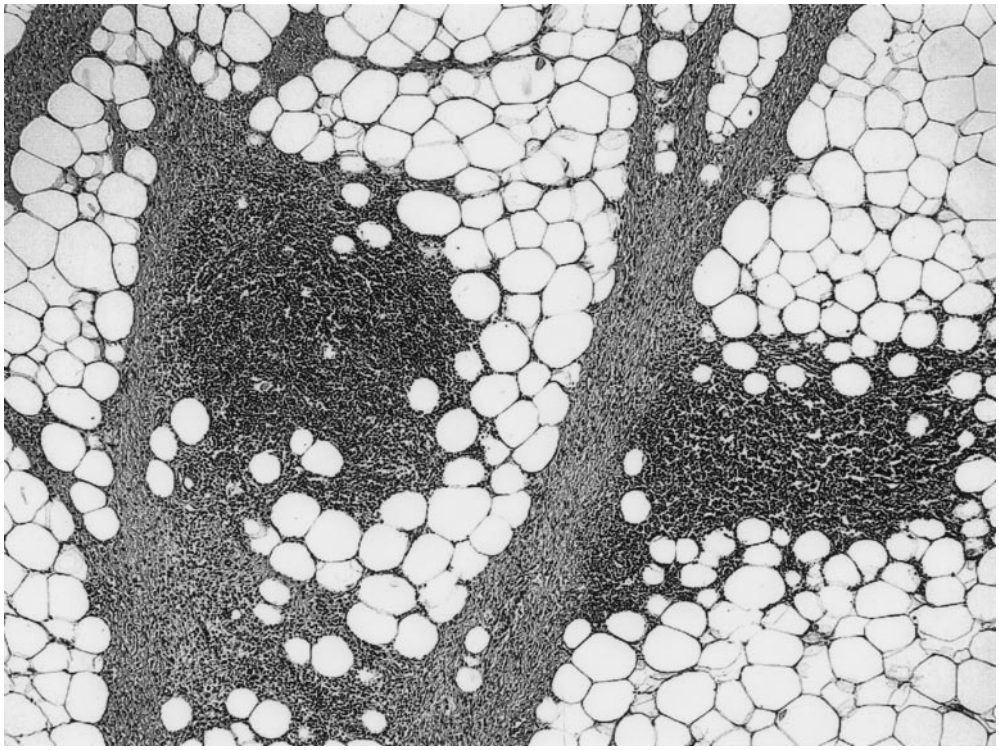

Fig. 4 An inflammatory-type liposarcoma (case 5) is marked by a dense inflammatory infiltrate consisting chiefly of lymphoid cells and plasma cells. Because of the rarity of typical lipoblasts, this type is easily confused with either lipoma or lipogranulomatous lesions. Haematoxylin and eosin, ×72

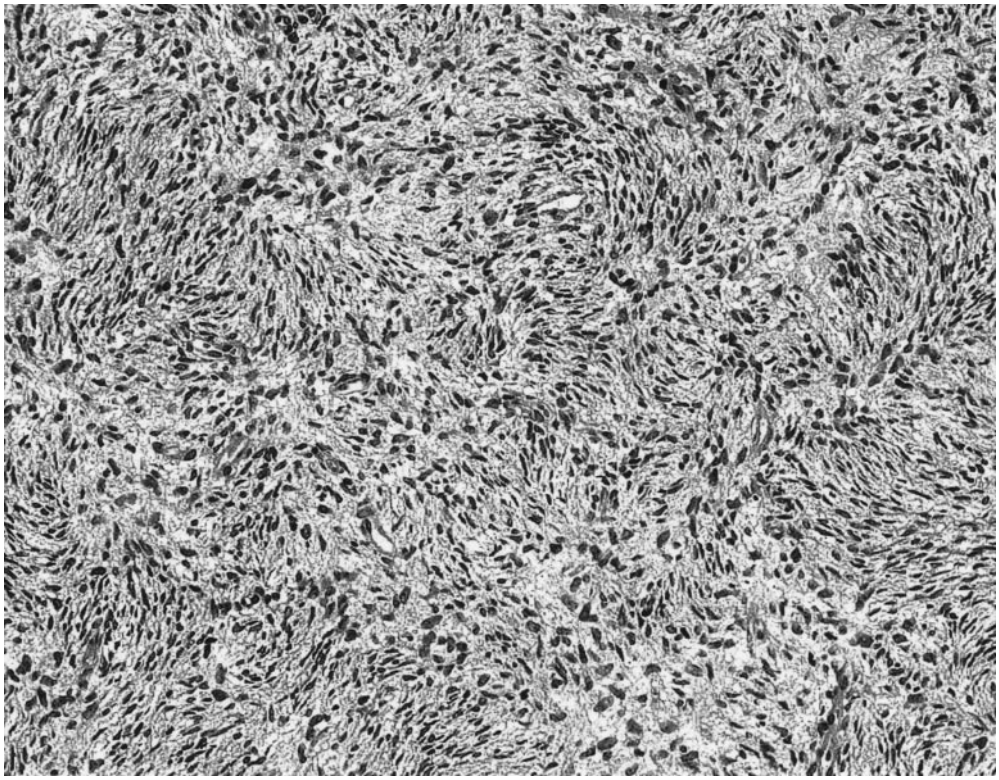

Fig. 5 DFSP is composed of uniform but atypical spindle cells arranged in a characteristic storiform pattern. Haematoxylin and eosin, ×180

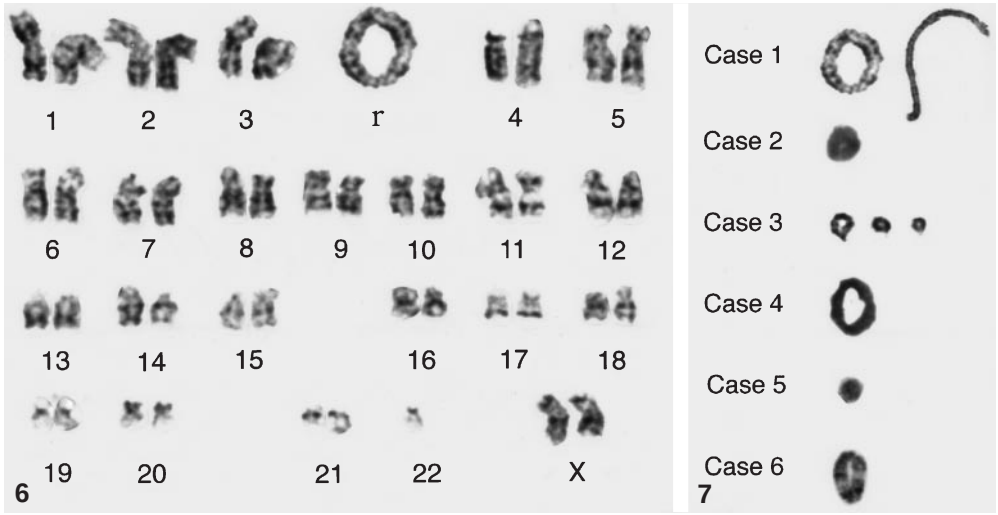

Fig. 6 A representative G-banded karyotype from an atypical lipomatous tumour (case 1) showing a ring chromosome. The loss of chromosome 22 was seen in this metaphase alone

Fig. 7 Partial karyotypes from 6 patients with atypical lipomatous tumour (cases 1 to 5) and dermatofibrosarcoma protuberans (case 6) showing ring chromosomes demonstrating a pattern of abnormally banded regions (*ABR*). In addition, a giant marker chromosome was observed in one metaphase cell in case 1

The inflammatory type (case 5) was marked by a dense inflammatory infiltrate consisting chiefly of lymphoid cells and plasma cells, accompanied by reactive lymphoid follicles, within a background of lipoma-like ALT (Fig. 4). Because typical lipoblasts were so rare, it was easy to confuse this tumour with lipoma or a lipogranulomatous lesion.

In the remaining case of DFSP, an elevated nodular lesion was found in the dermis with focal extension to the subcutaneous fat. Histologically, the tumour was composed of uniform but atypical spindle cells arranged in a characteristic storiform pattern (Fig. 5).

Supernumerary ring chromosomes were found in 6 cases of soft-tissue tumour: 5 cases of ALT (well-differentiated liposarcoma, 4; atypical intramuscular lipoma, 1) and 1 case of DFSP (Table 1). The size and inner structures of the ring varied from case to case (Figs. 6, 7). In 2 cases of ALT (cases 1 and 2), the ring chromosome was found to be the sole clonal abnormality, although a giant marker chromosome was observed as a nonclonal abnormality in case 1 (Fig. 7). The other 3 ALTs (cases 3, 4 and 5) exhibited composite karyotypes with one to three ring chromosomes and some additional minor abnormalities (Table 1). DFSP possessed a ring

chromosome without any other cytogenetic abnormalities (Fig. 7). In none of the cases could the G-band technique identify the origin of any of the ring or giant marker chromosomes, all showing a patten of abnormally banded regions (ABR).

Among the remaining 117 samples of soft-tissue tumours, 1 case of malignant fibrous histiocytoma possessed a ring chromosome, but this ring was associated with very complex karyotypic aberrations. Other types of tumour examined in this study demonstrated neither ring nor giant marker chromosomes.

By a FISH analysis applied on the rest of chromosomal samples from ALTs, the ring chromosome of 1 ALT (case 4) was successfully painted over its entire length with the chromosome 12 WCP probe (Fig. 8). Although the FISH samples from the remaining patients failed to demonstrate ring chromosomes, each ALT showed nuclear blebs and micronuclei containing chromosome 12 material (Fig. 9).

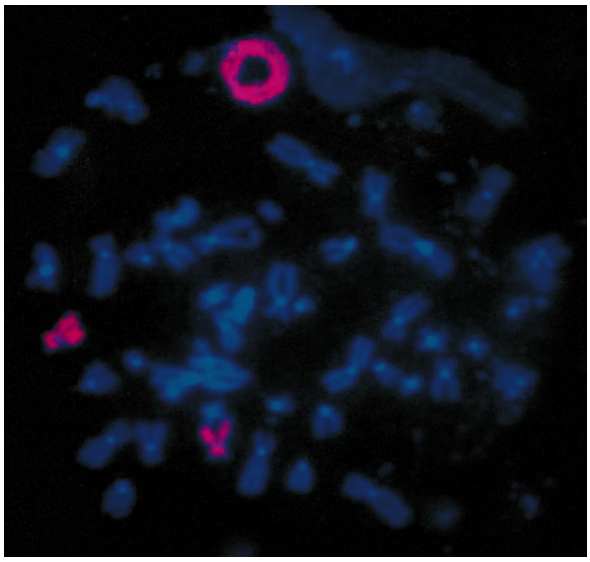

Fig. 8 The ring chromosome from a well-differentiated liposarcoma (case 4) is painted over its entire length with the chromosome 12 probe. FISH analysis, ×1,600

Discussion

In the present study, supernumerary ring chromosomes were found in 6 soft-tissue tumours. In addition, a giant marker chromosome was observed in one metaphase of atypical intramuscular lipoma. Among the remaining 117 samples of soft-tissue and bone tumours, 1 malignant fibrous histiocytoma had a ring chromosome, but this ring was associated with very complex karyotypic aberrations, thus presenting a sharp contrast to ALT and DFSP with their otherwise simple cytogenetic abnormality. The other cases of bone and soft-tissue tumours in our series demonstrated neither ring nor giant marker chromosomes. These results suggest a close relationship between the supernumerary ring or giant marker chromosomes and the pathogenesis of low-grade malignant soft-tissue neoplasms. The present study is the first report from the Asian region of ring and giant markers in low-grade soft-tissue tumours. No racial or geographic differences are thought to exist regarding the occurrence of ring chromosomes in low-grade soft-tissue neoplasms, and the results in this Japanese series are in keeping with the recent reports from the United States and Europe [3, 7, 9, 29, 34].

The histological recognition of ALT is often very difficult, especially when the tumour contains a limited number of atypical cells or lipoblasts in a background of predominant mature fat cells [1, 2, 5, 6, 12, 13, 18, 39]. In our case 1, the tumour showed features of intramuscular lipoma with minimal atypia, consisting almost entirely of mature fat cells. Only after a close examination of multiple sections were a few atypical cells detected, although no typical lipoblasts were observed. In such instances, the identification of supernumerary ring or giant marker chromosomes may help histopathologists, who often worry about the diagnosis of ALT. Atypical intramuscular lipoma and well-differentiated liposarcoma share supernumerary ring or giant marker chromosomes and clinicopathological features in many respects, although the number of atypical cells or lipoblasts is much fewer in the former than in the latter. Based on these findings, atypical lipoma and well-differentiated liposarcoma should thus be included in the same category as ALT [7, 29].

The inflammatory type of ALT causes another challenging problem for diagnostic pathologists, since the tu-

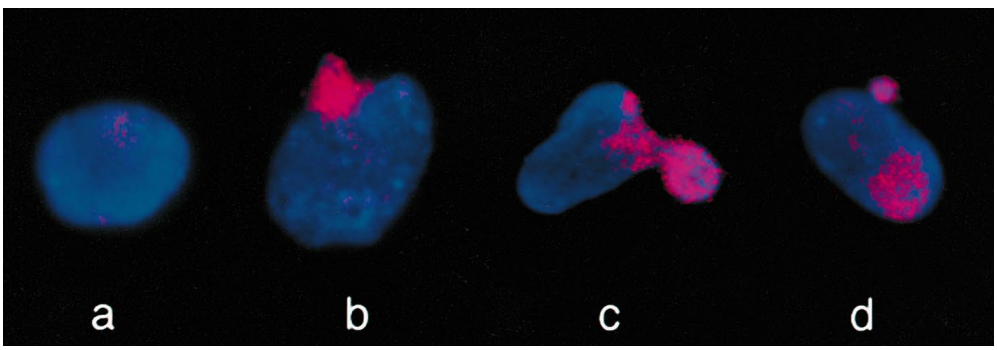

Fig. 9 **a** Normal nucleus. **b**, **c** Nuclear blebs and **d** micronucleus contain dense aggregates of chromosome 12 material. FISH in the interphase nuclei of well-differentiated liposarcoma, ×1,000

mour is often marked by a dense inflammatory infiltrate within a background of bland-looking lipomatous features [1, 5, 13]. Because typical lipoblasts are so rare, this type is easily confused with either lipoma or a lipogranulomatous lesion, but the cytogenetic analysis may be helpful in the diagnosis of such difficult cases.

The ring and giant markers may also help distinguish ALT from other benign lipomatous tumours, especially lipoblastoma/lipoblastomatosis and spindle cell/pleomorphic lipomas, which often have ALT-like features. Lipoblastomas show a specific 8q rearrangement involving the chromosome 8q11-13 region [4, 18, 23], while spindle cell/pleomorphic lipomas are characterized by loss of 16q13-qter [4, 7, 15, 18]. However, the ring or giant markers are never the characteristic features of these benign lipomatous tumours. Although rare cases of spindle cell/pleomorphic lipomas with ring chromosome have been reported [7, 15], more detailed clinical, histological and cytogenetic studies are required to determine whether there is a transition between ALT and spindle cell/pleomorphic lipomas.

Recent chromosome painting with the FISH technique has demonstrated that the ring and giant marker chromosomes in well-differentiated liposarcoma are chiefly composed of chromosome 12 sequences [3, 28, 36]. Our chromosome painting results confirmed the presence of chromosome 12 material in the ring chromosome in ALT. Micronuclei and nuclear blebs, which were also positive for chromosome 12 material, may therefore represent a topological distribution of ring or giant marker chromosomes in the interphase nuclei. The blebs, also called “projections” or “buds”, have been reported in cell lines possessing an extra-long chromosome 12 [28]. It has been proposed that blebs are precursors of micronuclei [28]. These blebs and micronuclei may be utilized as an alternative marker for ALT when typical ring or giant marker chromosomes cannot be detected due to insufficient sampling. Pedeutour et al. observed the inclusion of a chromosome 1, 4, and 12 sequence in micronuclei and in blebs, thus suggesting the elimination of supernumerary chromosomes in the micronuclei via the formation of blebs [28]. Moreover, their molecular studies with Southern blotting also demonstrated that well-differentiated liposarcomas show constant amplifications of *SAS* and *MDM2* genes, both of which are mapped to chromosome 12q13-q14. However, *GADD153/CHOP*, which is critically rearranged in myxoid liposarcoma, is not amplified in ALT [28]. These differences at the molecular level may contribute to the differences in the clinical and histological features between ALT and myxoid liposarcoma.

DFSP is a low-grade malignant tumour arising in the dermis, which produces an elevated nodular mass with frequent ulcerations on the surface of the epidermis [5]. Since the tumour often invades the adjacent subcutaneous fat, local recurrences are common after surgical excision. Histologically, DFSP is composed of uniform but atypical spindle cells forming a characteristic storiform pattern. The origin and true nature of the tumour cells are still unknown. Although DFSP has traditionally been classified as a fibrohistiocytic neoplasm, some investigators have also suggested either a neurogenic or perineural origin for this tumour [8, 38]. In the present study, DFSP was characterized by the presence of supernumerary ring chromosomes in the context of noncomplex karyotypes. Recently, a FISH analysis and comparative genomic hybridization [20, 21, 26, 27] demonstrated that the ring chromosomes of DFSP contain the chromosome 22 centromere along with interstitial sequences from chromosomes 17 and 22, specifically from regions 17q23-24 and 22q11-12. The alterations in proximal 22q have often been observed in tumours, especially in tumours of neural origin [26, 30, 37]. This finding may provide some clue to the histogenesis of DFSP, and possibly support its neural or perineural origin. However, more recent FISH and genomic studies [27, 31] have demonstrated that DFSP is characterized by t(17;22)(q22;13) and supernumerary ring chromosomes derived from the t(17;22) and that these rearrangements fuse the platelet-derived growth factor B-chain (*PDGFB, c-sis* proto-oncogene) and the collagen type I α1 (*COL1A1*) genes [31]. *PDGFB* has transforming activity and is a potent mitogen for a number of cell types, whereas *COL1A1* is a major constituent of the connective tissue matrix.

In conclusion, our findings suggest that supernumerary ring chromosomes are characteristic of some low-grade soft-tissue neoplasms, including ALT and DFSP. A cytogenetic analysis may therefore prove to be helpful in diagnosing difficult cases of low-grade neoplasm. The nuclear blebs and micronuclei may be utilized as an alternative marker when typical ring or giant marker chromosomes cannot be detected owing to insufficient sampling.

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