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Translocation of the *HMGI-C (HMGA2)* gene in a benign mesenchymoma (chondrolipoangioma)

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Abstract Mesenchymomas are neoplasms in which there are at least two types of differentiated cells of mesenchymal derivation other than fibrous tissue. Chondrolipoangioma is a rare type of mesenchymoma composed predominantly of cartilage and adipose tissue with vascular elements and myxoid tissue present in lesser proportions. Cytogenetic analysis was performed on a case of chondrolipoangioma and revealed a t(12;15) (q13;q26) as the sole chromosome abnormality in 40 metaphases analyzed. However, using fluorescence in situ hybridization (FISH) analysis, a complex rearrangement was found involving chromosomes 2, 12, and 15, with a cryptic rearrangement of the gene (*HMGI-C; HMGA2*) coding for high-mobility group I protein. This finding suggests a role for the *HMGI-C* gene also in the pathogenesis of this uncommon benign tumor type, in addition to its well-established role in the pathogenesis of common benign tumors such as lipomas, uterine leiomyomas, pulmonary chondroid hamartomas, and endometrial polyps.

Keywords Chondrolipoangioma · Cartilage-containing benign mesenchymoma · Fluorescence in situ hybridization · Conventional cytogenetic analysis · *HMGI-C* · *HMGA2*

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Introduction

Mesenchymoma was established as a distinct pathological entity by Stout in 1948 [16]. He defined it as a distinct neoplasm composed of two or more mesenchymal elements not ordinarily found together in a tumor – such as bone and cartilage. “Undifferentiated” and “fibrosarcomatous” or “fibrous” areas are present in a wide range of mesenchymal tumors and therefore must not be counted as one of the components [11]. Stout's original article dealt only with malignant tumors, but he stated that the tumor occurred in both benign and malignant forms. Benign mesenchymoma constitutes a heterogeneous group of tumors. Angiomyolipomas, angioliipomas, and chondrolipomas could be described as benign mesenchymomas, but the term is more often used for rare tumors with a complex mixture of mesenchymal tissues. A subgroup of benign mesenchymomas are composed of cartilage, mature fat, and vascular elements and can be described as chondrolipoangiomas (or cartilage-containing benign mesenchymomas) [3, 9]. To the best of our knowledge, cytogenetic analysis of this type of benign mesenchymoma has not been reported previously. Here, we report a benign mesenchymoma (chondrolipoangioma) exhibiting a t(12;15)(q13;q26) with a cryptic rearrangement of the gene (*HMGI-C; HMGA2*) coding for the high-mobility group I protein.

Clinical history

A 50-year-old man presented with a painless mass in the right buttock, which had been present for several months, causing numbness of the right leg when sitting down. Physical examination revealed a mass with a diameter of 8 cm located posterior to the greater trochanter of the right hip. Motor and sensory examination of the right leg were normal. Plain radiographs revealed a partially calcified mass adjacent to the right hip. Magnetic resonance imaging showed a well-circumscribed partially calcified mass deep in the gluteal muscles, posterior to the femoral neck and lateral to the sciatic nerve. Metastatic work-up of the lungs, liver, and bones was negative. An incisional biopsy was performed. The biopsy showed “neoplastic” fat and myxoid tissue with calcifications. A

definitive diagnosis was not possible on this material. The tumor was completely excised with a rim of uninvolved muscle and soft tissue. The patient was without evidence of recurrence 4 years postoperatively.

Materials and methods

The incisional biopsy and the resection specimen were received fresh. Fragments from the incisional biopsy and from the lesion in the resection specimen were used for short-term culturing (4 days) after overnight disaggregation with collagenase, as described previously [8, 12]. Chromosome analysis was performed on G-banded metaphases. The remaining tissue was fixed in neutral buffered formalin (6%). Ossified parts of the resection specimen were decalcified in ethylene diamine tetraacetic acid (EDTA) after fixation. Multiple tissue blocks were embedded in paraffin, cut to 5 μ m, and stained with hematoxylin and eosin. Selected paraffin sections were immunohistochemically stained with antibodies against S100 protein (polyclonal, 1:500; Dako, Glostrup, Denmark), alpha smooth muscle actin (monoclonal antibody, 1:200; Sigma, St. Louis, Mo.), desmin (monoclonal antibody, 1:20; Eurodiagnostics, Apeldoorn, the Netherlands), cytokeratin (monoclonal antibody KL1, 1:75; Immunotech, Marseille, France), and epithelial membrane antigen (monoclonal antibody, 1:50; Dako) using a three-step immunoperoxidase procedure.

Fluorescence in situ hybridization (FISH) with biotin- and digoxigenin-labeled cosmids 142H1 and 27E12, which map to the 5' and 3' region of the *HMGJ-C* gene, respectively, was performed on metaphase spreads from the tumor culture, as previously described [19]. Further FISH investigation was performed on the same tumor metaphase cell spreads with the alpha satellite DNA probes specific for the centromeric region of chromosomes 1, 2, and 3 (A-group chromosomes; Oncor, Gaithersburg, Md.).

Results

The incisional biopsy had a diameter of 1.5 cm and consisted of adipose tissue showing fat cells of varying diameters and myxoid tissue. The resection specimen contained a 10 \times 7 \times 7-cm measuring mass (Fig. 1). The mass was well circumscribed and could be enucleated from the surrounding skeletal muscle. The cut surface had a variegated appearance. Fat, cartilage, and bone could be recognized macroscopically. Rare small cysts were seen in the cartilaginous areas. The tumor was extensively sampled for microscopic analysis. Histologically, mature adipose tissue and cartilage were the two predominant tissues (Fig. 2). Other components of the tumor were myxoid tissue, bone, fibrous tissue, smooth muscle, and aberrant blood vessels. The different components were intermixed in a haphazard fashion. The adipose tissue consisted of irregular lobules separated by incomplete fibrous septa of varying thickness (Fig. 2a). The fat cells showed some variation in size and shape. Lipoblasts, however, were not present. Cell nuclei were eccentrically placed, small, and flattened. Nuclear atypia was not seen. Large areas of the adipose tissue had a prominent myxoid matrix, but a delicate plexiform capillary pattern typical for myxoid liposarcoma was not present. The areas with cartilaginous differentiation were intermingled with the adipose tissue. There were

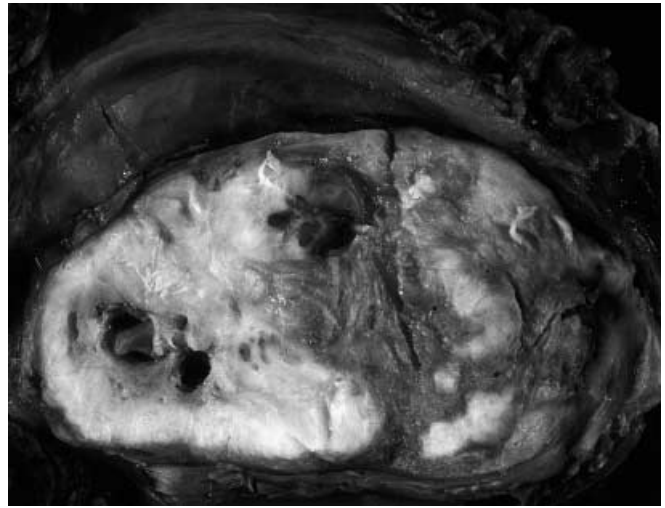
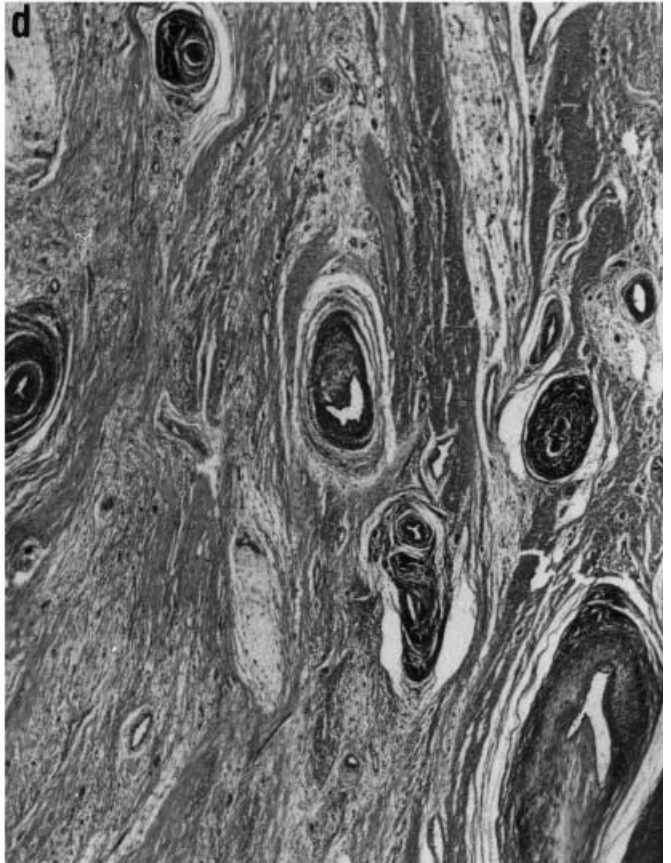
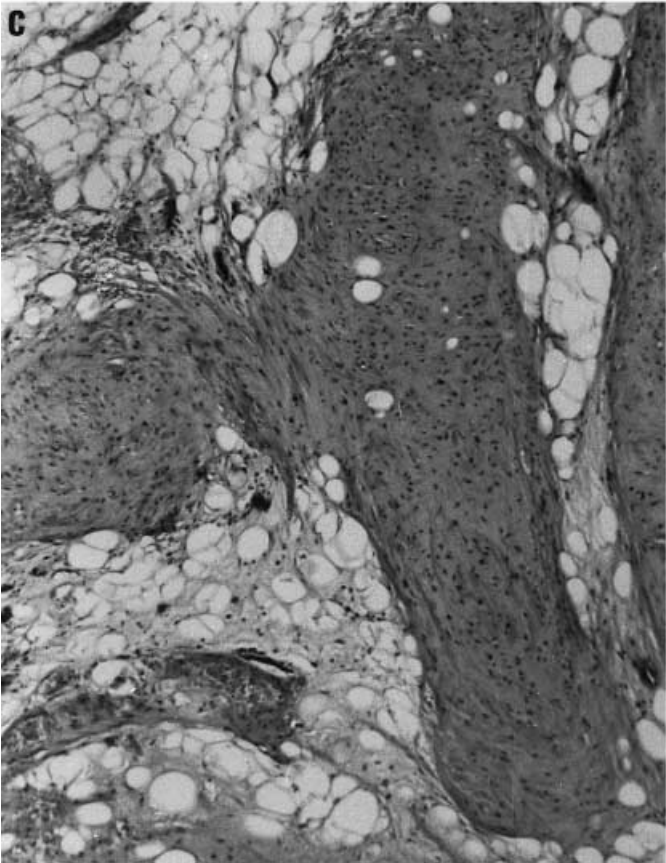
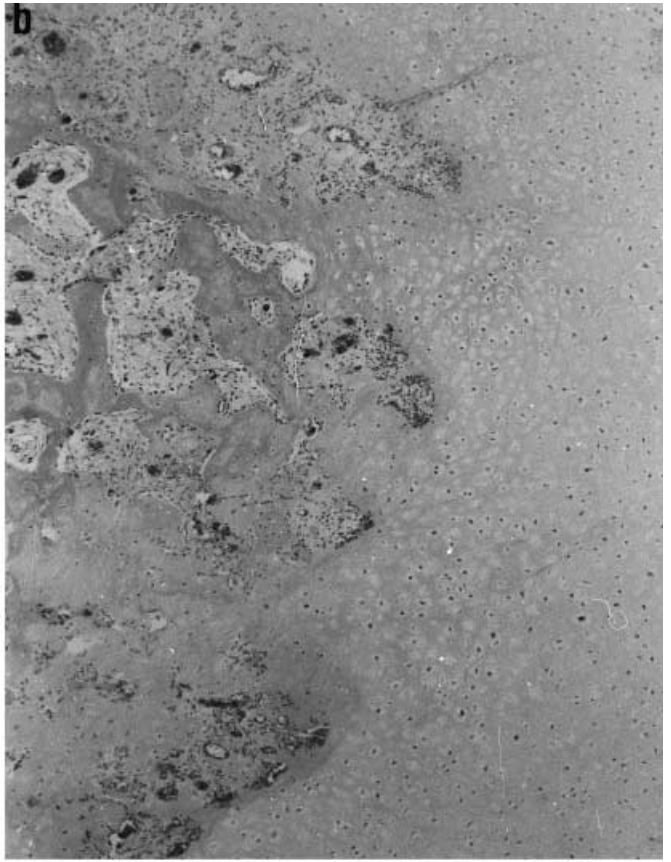
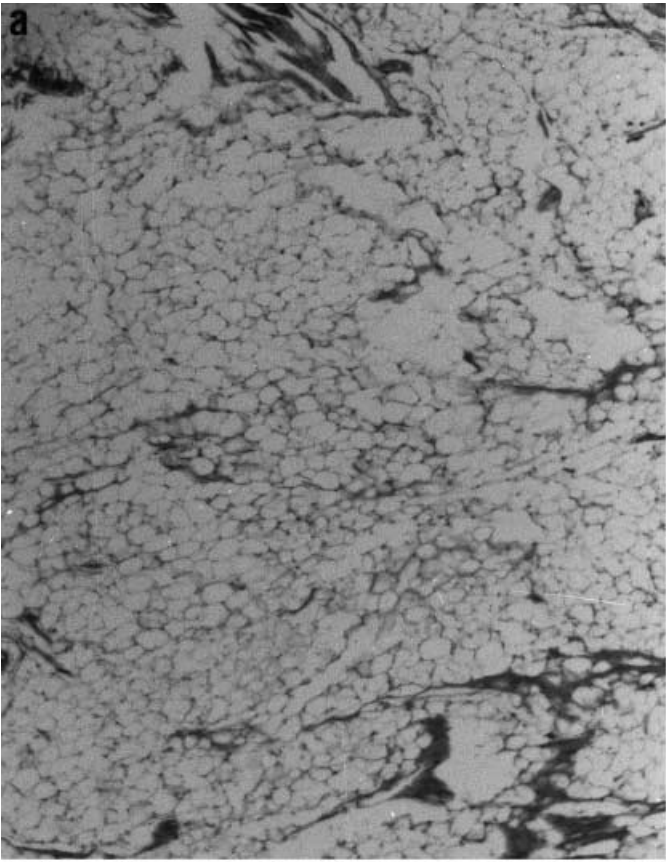


Fig. 1 The tumor is well circumscribed. The cut surface has a variegated appearance. Fat and cartilage are the main components and can be recognized macroscopically

chondromyxoid areas as well as large areas of mature hyaline cartilage (Fig. 2b, c). The hyaline cartilage showed foci with increased cellularity, but there was only minimal pleomorphism, and mitoses were absent. Areas of ossification consisting of mature trabecular bone and intertrabecular mature fat were present in the cartilage (Fig. 2b). The myxoid component was moderately cellular and was composed of delicate spindle or stellate cells and abundant mucoid material. In most areas, there was a gradual transition between myxoid tissue, adipose tissue (adipose tissue with myxoid matrix), and cartilage (chondromyxoid areas). The adipose tissue and the myxoid tissue showed angiomatous areas with dilated thin-walled vessels and abnormally formed, thick-walled vessels; the vascular lumina were sometimes eccentrically placed (Fig. 2d). Irregularly distributed compact bundles of smooth muscle cells and fibrous septa were present in the angiomatous areas. A rim of compressed fibrous tissue was present at the periphery of the tumor. Immunohistochemical staining for alpha smooth muscle actin and desmin confirmed the presence of compact bundles of smooth muscle cells. The chondrocytes and adipocytes stained for S100 protein, but the spindle cells did not show neural differentiation. Staining for cytokeratin and epithelial membrane antigen was negative.

All 40 G-banded metaphases obtained from 3-day-old cultures of both the incisional biopsy and the lesion in the resection specimen showed a t(12;15)(q13;q26) as

Fig. 2 **a** Low-power view showing adipose tissue. The fat lobules are irregular and separated by incomplete fibrous septa. Hematoxylin and eosin (HE), \times 26. **b** Low-power view showing hyaline cartilage and mature trabecular bone. HE, \times 26. **c** Chondromyxoid tissue and adipose tissue with a myxoid matrix. HE, \times 42. **d** Fibrous tissue with numerous abnormally formed, thick-walled vessels (angiomatous tissue). HE, \times 42



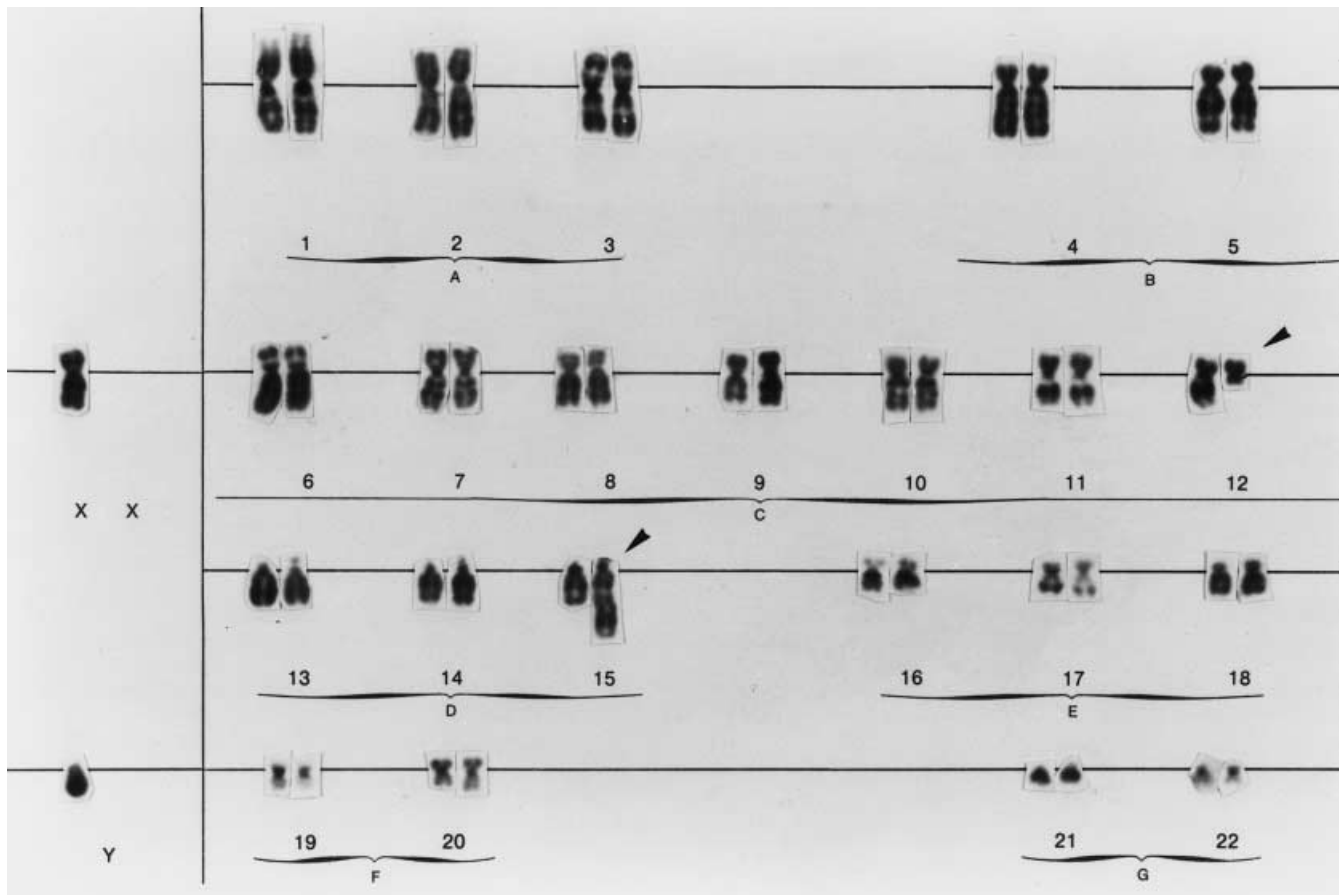


Fig. 3 G-banded metaphase showing $t(12;15)(q13;q26)$

the sole chromosomal abnormality (Fig. 3). A normal male karyotype was found on phytohemagglutinin (PHA)-stimulated peripheral lymphocytes.

FISH analysis performed with *HMGI-C* specific cosmids 142H1 (5') and 27E12 (3') revealed an unexpected (cryptic) complex chromosome rearrangement. Both cosmids hybridized to the normal chromosome 12 and to an unidentified A-group chromosome (data not shown). This chromosome was subsequently identified using FISH as derivative chromosome 2, der(2), using the 27E12 cosmid and the chromosome-specific alpha satellite DNA probe (D2Z; Oncor) (Fig. 4a, b). The breakpoints at chromosome 12 occurred at the 5' end of the *HMGI-C* proximal to the 142H1 cosmid and at the 3' end of the *HMGI-C* distal to the 27E12 cosmid, resulting in translocation of the entire *HMGI-C* gene to the telomeric region of the long (q) arm of derivative chromosome 2, der(2). The remaining 12q was subsequently translocated to the 15q26 band, as suspected by conventional cytogenetic analysis.

Discussion

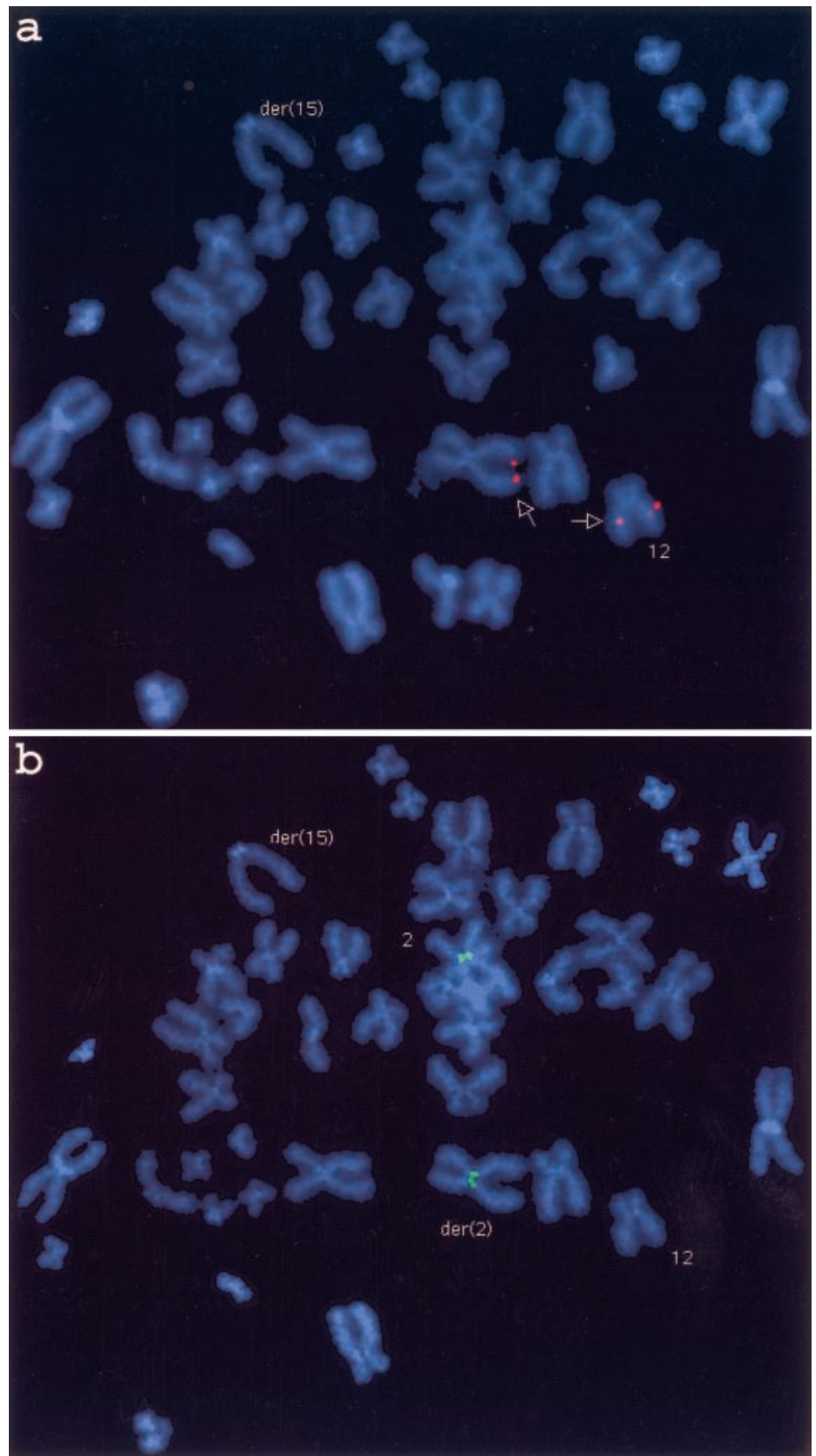
The tumor had the typical features of a lesion reported variably in the literature as chondrolipoangioma [9] or

cartilage-containing benign mesenchymoma [3] and fitted the definition of benign mesenchymoma [16]. The chondrolipoangioma contained fat cells with some variation in size and shape and cartilage with foci of increased cellularity, but morphological indicators to support a diagnosis of liposarcoma, such as lipoblasts, significant nuclear pleomorphism, increased mitotic activity, or infiltration, were absent [4]. Foci of hyaline cartilage have been reported in some myxoid liposarcomas, but other patterns of mesenchymal differentiation were not present in these cases [15].

Ten well-documented cases of chondrolipoangioma have been reported in the literature [1, 3, 5, 7, 9, 14, 17]. Patients with a chondrolipoangioma have ranged in age from 7 years to 55 years. Most chondrolipoangiomas are well circumscribed and occur in the soft tissues of the limbs or the trunk. Recurrences or malignant behavior have never been reported. Some authors consider benign mesenchymomas to be hamartomatous malformations [2], but the presence of a clonal chromosomal aberration in the present case supports the neoplastic nature of chondrolipoangiomas. Malignant transformation has never been reported in a benign mesenchymoma [3].

The genes coding for the HMGI proteins, *HMGI-C* (*HMGA2*) on chromosome 12q15 and *HMGI(Y)* (*HMGA1b*) on chromosome 6p21, are increasingly implicated in the pathogenesis of a variety of malignant and benign tumors [18]. Specific chromosomal rearrange-

Fig. 4 **a** Representative tumor metaphase cell showing the hybridization signals (*red*) for cosmid 27E12, specific for the 3' end of the *HMGI-C*, on the normal chromosome 12 and one of the A-group chromosomes (*arrows*). **b** Same metaphase cell hybridized with alpha satellite probe specific for the centromeric region of chromosome 2 (D2Z; Oncor). Hybridization signals are present on a normal chromosome 2 and on the derivative chromosome 2, *der*(2), carrying the *HMGI-C* gene



ments involving the *HMGI-C* or *HMGI(Y)* gene are the most frequent chromosomal alterations in common benign tumors such as lipomas, uterine leiomyomas, hamartomas of the lung and breast, fibroadenomas of the breast, pleomorphic adenomas of salivary gland, and endometrial polyps. In the present case, FISH analysis showed a complex rearrangement involving chromosomes 2, 12, and 15, resulting in translocation of an entire copy of the *HMGI-C* gene. Rearrangements of the *HMGI-C* gene in benign tumors often result in intragenic rearrangements leading to chimeric fusion products, but transfer of the entire coding region of the gene (5' break of the *HMGI-C* gene), as seen in this chondrolipoangioma, have also been reported in other benign tumors, such as pulmonary chondroid hamartoma [6], but most commonly in uterine leiomyomas [13]. It is thought that translocation of the *HMGI-C* gene results in deletion of silencer promoter elements or in juxtaposition to enhancer elements leading to dysregulation of *HMGI-C* expression.

Although uncommon, complex rearrangements involving the *HMGI-C* gene are sometimes seen in other benign tumors such as uterine leiomyomas and lipomas [10]. Interestingly, in these tumors the complex rearrangements do not seem to correlate with any histopathologic or clinical feature. In conclusion, we report translocation of the *HMGI-C* gene in a rare benign mesenchymoma. The finding of this rearrangement also in uncommon tumors with distinctive morphology underscores the important and widespread role of *HMGI* genes in the pathogenesis of human neoplasia.

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