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Hyperhaploid uterine mesenchymal tumors —a novel genetic subgroup?

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Hyperhaploid karyotypes have been described to occur in subsets of various solid tumors and leukemias. In these cases, monosomy is noted for most of the chromosomes while a few chromosomes still remain disomic. Evidence has emerged that at least in some tumor entities these remaining chromosomes are non-randomly selected. In addition, structural alterations can accompany the reduced chromosome number and secondary duplication of the chromosome complement is also a frequent finding. In this report, we describe hyperhaploidy in a case of an endometrial stromal nodule of a 50 year old woman who underwent hysterectomy because of symptomatic uterine fibroids. In addition, we review two other recently described cases of uterine mesenchymal tumors with that type of genetic alteration. Despite some histologic differences, striking similarities between these three cases exist with respect to the chromosomes were retained as disomic. Thus, the question arises if hyperhaploidy defines a novel genetic subgroup of uterine mesenchymal tumors.

Keywords Hyperhaploidy, uterine mesenchymal tumors, endometrial stromal tumor, genetic classification, molecular inversion probe array

Introduction

Hyperhaploid karyotypes (24–34 chromosomes) are seen in a variety of human tumors as e.g. ALL, myeloid leukemias, plasma cell neoplasms (1), as well as malignant epithelial tumors. While hyperhaploidy in general is a rare finding in most tumors, hyperhaploidy to near diploidy may be frequent in particular tumor entities as e.g. chondrosarcomas where it even accounts for about one half of the lesions (2).

In nearly all of the hyperhaploid tumors some chromosomes remain disomic. Evidence has emerged that these chromosomes are non-randomly selected depending on the tumor entity (1,3). Recently, hyperhaploidy for the first time has been reported in a uterine leiomyosarcoma studied by copy number variation array analysis (4) and, by the same method, a case of an epithelioid uterine leiomyoma was studied that revealed uniparental disomy for most of the chromosomes (5). In that latter case, the findings were explained by the initial presence of a hyperhaploid chromosome number followed by secondary duplication of the chromosomes. Herein, we report an endometrial stromal nodule (ESN) representing a further hyperhaploid mesenchymal uterine tumor. While the tumor reported here was histologically different from the two previous cases, all three tumors showed considerable genetic similarities. Herein, we would like to consider the existence of a novel genetic subgroup of hyperhaploid uterine mesenchymal tumors with varying histologic differentiation depending on the presence of additional genetic abnormalities.

Materials and methods

A 50 year old patient was admitted to the hospital for hysterectomy because a histologic examination of a sample obtained by previous curettage had revealed evidence for an endometrial stromal tumor (EST). Following surgery a 7.7 cm tumor (largest diameter) presumably of uterine smooth muscle origin was identified, fixed in paraformaldehyde (4% in PBS), and processed for paraffin embedding. Tissue sections (1–2 μm) were de-paraffinized in xylene, rehydrated through a series of ethanol, and stained with hematoxylin and eosin (H&E) for histological examination. Histologically, the well-demarcated lesion (Figure 1A) measuring 7.7 cm (largest diameter) presented with high cellularity and areas of thick-walled vessels

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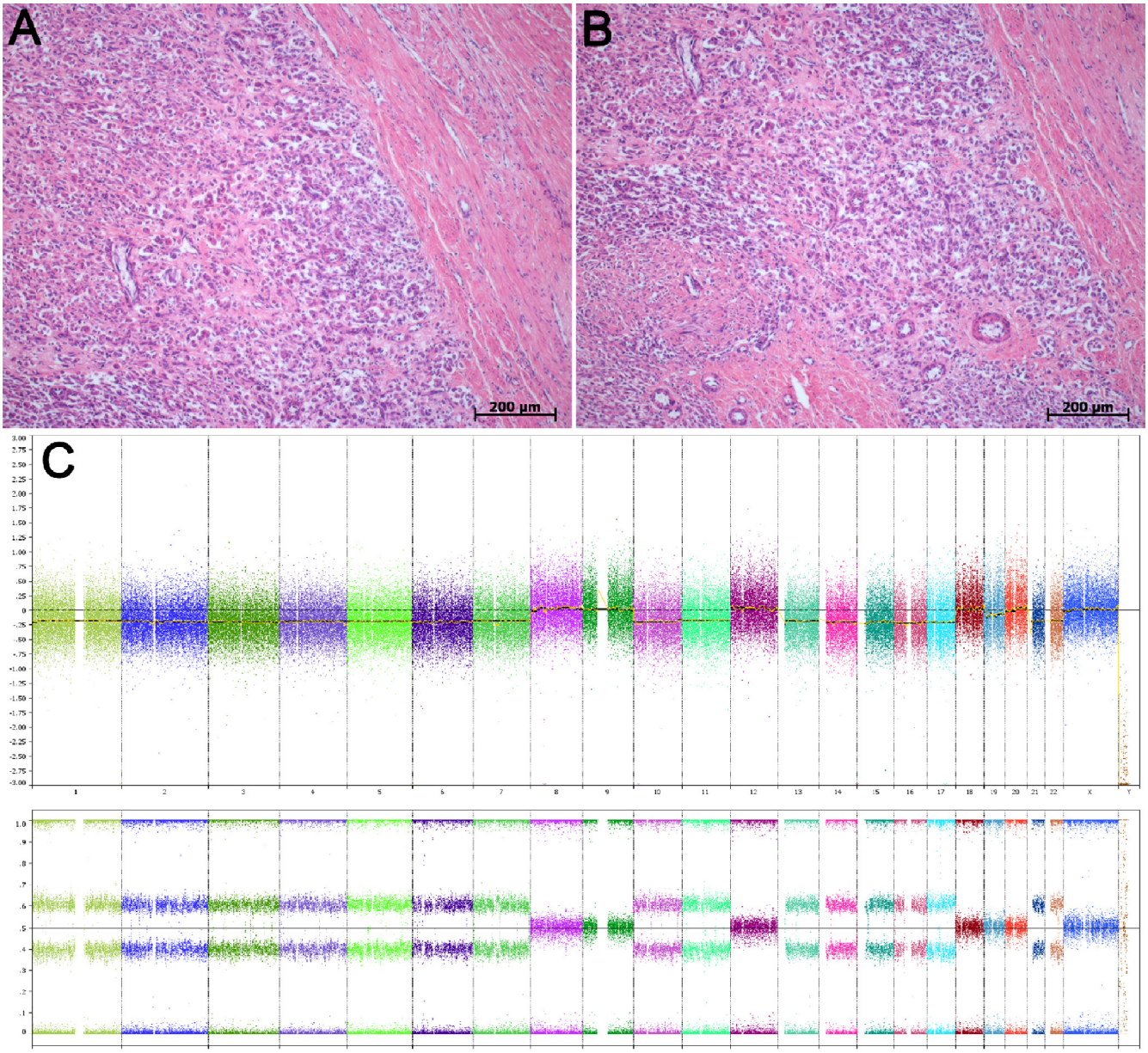

Figure 1 Histology and array-based karyotype of the tumor. (A) Hematoxylin/eosin stained tissue section showing a well-demarcated tumor with high cellularity and (B) areas of thick-walled vessels. (C) CNV array analysis of the tumor revealed a hyperhaploid karyotype. The result of the copy-number probes (upper panel) is confirmed by the B-allele frequency (BAF) plot of the SNP probes (lower panel). Disomic areas of chromosomes display log ratios centered on 0 on the Y axis and three tracks in the BAF graph. In contrast, the hyperhaploid karyotype shows log ratios around –0.2 and four tracks in the BAF graph indicating the presence of hyperhaploid tumor cells along with contaminating normal cells.

(Figure 1B). Necrotic areas and those with bizarre nuclei were seen as well. Immunohistochemically, the lesion was positive for vimentin and CD10 and focally positive for desmin, caldesmon, and ER-alpha/ER-beta. In addition, a very weak expression of pancytokeratin but not of CK5/6 and CK7 was noted. In the absence of lymphovascular invasion the lesion was classified as an endometrial stromal nodule (ESN). For further characterization the tumor was investigated in addition by genetic analyses.

DNA from the FFPE samples was isolated using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) on a QIACube (Qiagen), according to the manufacturer's instructions. The amount of double-stranded DNA was measured using the Qubit dsDNA HS Assay Kit and a Qubit Fluorometer (Life Technologies, Carlsbad, CA, USA).

Analysis for mutations of *MED12* using isolated DNA and MIP assay and array hybridization were performed as described recently (4,6,7). The OncoScan FFPE Assay (Affymetrix, Santa Clara, CA) results in a 300-kb genome-wide copy number resolution and an enhanced copy number resolution of 50–100 kb in ~900 cancer genes. Labeling of 80 ng dsDNA and array hybridization was done following the