Genetic Characterization of Myoid Hamartoma of the Breast

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Abstract. *Background/Aim:* Myoid hamartoma of the breast is a very rare benign lesion of which only a few cases have been reported. The pathogenesis is unknown and nothing is known about its genetic constitution. We report here the genetic characterization of a myoid hamartoma of the breast. *Materials and Methods:* Cytogenetic, fluorescence in situ hybridization (FISH), RNA sequencing, reverse transcription polymerase chain reaction (RT-PCR), and Sanger sequencing analyses were performed on a myoid hamartoma of the breast. *Results:* G-Banding analysis of short-term cultured tumor cells yielded the karyotype 46,XX,t(5;12)(p13;q14)[6]/46,XX[4]. FISH showed rearrangement of the high mobility group AT-hook 2 (HMGA2) gene. RNA sequencing detected fusion of HMGA2 (12q14) with a sequence from 5p13. RT-PCR together with Sanger sequencing verified the HMGA2-fusion transcript. *Conclusion:* Myoid hamartoma of the breast may be pathogenetically related to benign connective tissue tumors with HMGA2 rearrangements, such as pulmonary hamartomas, lipomas, myolipomas, and leiomyomas.

Hamartoma is a benign tumor made up of an abnormal focal overgrowth of cells and tissues normally present in that part of the body. It can develop in various organs including the lungs, skin, hypothalamus and breast (1-4). The term ‘mammary

hamartoma’ was first used by Arrigoni *et al.* (5) to describe a well-circumscribed breast lesion with varying amounts of benign epithelial elements, fibrous tissue, and fat (5). Myoid (muscular) hamartoma of the breast was described 2 years later by Davies and Riddell (6) as a subtype of breast hamartoma characterized by the presence of smooth muscle cells. It is a very rare benign lesion of which only few cases have been reported (7-22). The pathogenesis is unknown and nothing is known about their genetic constitution. We report here the genetic characterization of a myoid hamartoma of the breast.

Materials and Methods

Ethics statement. The study was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, <http://helseforskning.etikkom.no>). Written informed consent to publication of the case details was obtained from the patient. The Ethics Committee’s approval included a review of the consent procedure. All patient information has been de-identified.

Patient. Routine examination of a 44-year-old female by her general physician detected a lump in the left breast. Radiological examination revealed a well-defined tumor measuring 57×31×42 mm. Upon mammography, the lump was translucent, whereas magnetic resonance imaging and ultrasound examination of the lump gave heterogeneous signals. The diagnosis on core-needle biopsy was leiomyomatous tumor of uncertain malignant potential. A lumpectomy was performed.

Microscopic examination of the specimen showed a well-demarcated lesion without capsule, consisting of alternating areas of glandular, fat and smooth muscle tissue (Figure 1A-C). The latter component was quite prominent, displaying tightly packed bundles of smooth muscle cells showing immunohistochemical positivity for the muscle markers desmin and smooth muscle actin (Figure 1D). The glandular tissue displayed clefts in the fibrous stroma consistent with pseudoangiomatous stromal hyperplasia (Figure 1A and B). The fat tissue was pure in some areas, and scattered, single fat cells in others (Figure 1C). No atypia was seen, nor were any mitoses detected in any component. The final diagnosis was myoid hamartoma.

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Key Words: Myoid hamartoma of the breast, chromosome translocation, cytogenetics, HMGA2 rearrangement, fluorescence in situ hybridization, RNA sequencing, reverse transcription polymerase chain reaction, Sanger sequencing.

G-Banding and karyotyping. Fresh tissue from a representative area of the tumor was analyzed cytogenetically as part of our diagnostic routine. The samples were disaggregated mechanically and enzymatically with collagenase II (Worthington, Freehold, NJ, USA). The resulting cells were cultured and harvested using standard techniques (23). Chromosomal preparations were G-banded with Wright's stain (Sigma Aldrich, St Louis, MO, USA) and examined. Metaphases were analyzed and karyograms prepared using the CytoVision computer assisted karyotyping system (Leica Biosystems, Newcastle-upon-Tyne, UK). The karyotypes were described according to the International System for Human Cytogenomic Nomenclature (24).

Fluorescence in situ hybridization (FISH). FISH analysis was performed on both interphase nuclei and metaphase plates (see below). A homemade high mobility group AT-hook 2 (*HMGA2*) break-apart probe was made from commercially available bacterial artificial chromosomes. The 5'-end of the probe (red signal) was constructed from a pool of clones RP11-185K16, RP11-30I11, and RP11-662G15. The 3'-end of the probe (green signal) was constructed from a pool of the clones RP118B13, RP11-745O10, and RP11-263A04. All of them map to chromosome subband 12q14.3 and cover the *HMGA2* locus. Detailed information about the probe is given elsewhere (25, 26).

RNA sequencing. Total RNA was extracted from frozen (−80°C) tumor tissue adjacent to that used for cytogenetic analysis and histological examination using miRNeasy Mini Kit (Qiagen Nordic, Oslo, Norway). One microgram of total RNA was sent to the Genomics Core Facility at the Norwegian Radium Hospital, Oslo University Hospital (<http://genomics.no/oslo/>) for high-throughput paired-end RNA-sequencing. For library preparation from total RNA, Illumina TruSeq RNA Access Library Prep kit was used according to Illumina's protocol (Illumina, San Diego, CA, USA (https://support.illumina.com/content/dam/illumina-support/documents/documentation/chemistry_documentation/samplepreps_truseq/truseqrnaaccess/truseq-rna-access-library-prep-guide-15049525-b.pdf)). Sequencing was performed on NextSeq 550 System (Illumina) and 25 million reads were generated. The software deFuse was used for detection of possible *HMGA2* fusion transcripts (27).

In order to confirm the existence of an *HMGA2* fusion with the sequence from chromosome band 5p13 (see below), reverse transcription (RT) polymerase chain reaction (PCR) and Sanger sequencing analyses were performed as previously described (26). The primers used were forward: *HMGA2*-929F1 (ACCGGTGA GCCCTCTCCTAAGAG) and reverse: 5p13R (GAAATGGGT CAGGCCTATCAGCA).

Results

G-Banding analysis yielded a karyotype with a single chromosomal abnormality: 46,XX,t(5;12)(p13;q14)[6]/46,XX[4] (Figure 2A). FISH analysis on metaphase spreads showed that the distal part of the *HMGA2* probe hybridized to the p13 band of der(5), whereas the proximal part of the probe hybridized to the q14 band of der(12) (Figure 2B). Interphase FISH showed two normal (yellow) signals in 48 nuclei and one yellow, one red, and one green signal (*i.e.* splitting of the *HMGA2* probe) in 39 nuclei.

Using the deFuse software on the fastq files of the RNA sequencing data, a fusion of *HMGA2* with a sequence from chromosome band 5p13.2 was found (Figure 2C).

RT-PCR with the primer combination *HMGA2*-929F1/5p13R amplified a 349 bp cDNA fragment (data not shown). Direct sequencing of the PCR fragment showed that it was an *HMGA2*-chimeric cDNA fragment (Figure 2D). The fusion point was identical to that found by analysis of the RNA sequencing data using the deFuse software. Thus, in the *HMGA2*-chimeric transcript, exon 3 of *HMGA2* (nt 1060 in reference sequence with accession number NM_003483.4) was fused with an intragenic sequence from chromosomal band 5p13.2 between the genes encoding prolactin receptor (*PRLR*) and sperm flagellar protein 2 (*SPEF2*). The *HMGA2*-truncated transcript codes for a putative protein which contains amino acid residues 1-83 of the *HMGA2* protein (accession number NP_003474.1) corresponding to exons 1-3 of the gene, and nine amino acid residues from the sequence derived from 5p13 (VHSTGEKQS) (Figure 2E).

Discussion

Although there is considerable information about the acquired genetic alterations of pulmonary chondroid hamartomas, corresponding information on hamartomas from other organs and tissues is still very limited (28). As far as we are aware, cytogenetic knowledge on hamartoma of the breast is restricted to only four cases (29-31). The first two tumors had the karyotypes 47,XX,del(1)(p22) and 46,XX,t(12;16)(q15;q24) (29). The third hamartoma had the karyotype 46,XX,add(4)(?),add(6)(q?),der(7)t(7;12)(q11;q11-12),der(12) (30). The breakpoint in 12q was found to be within the same region as are the 12q-breakpoints often found in other benign solid tumor types such as uterine leiomyomas, lipomas, and pleomorphic salivary gland adenomas (30). Cytogenetic changes of bands 12q13-15 are a recurrent theme in benign connective tissue tumors and have been shown to lead to rearrangement/activation of *HMGA2* (28). Finally, the fourth tumor had the karyotype 46,XX,t(1;6)(p21;p21) with rearrangement of *HMGA1* in 6p21 (31).

Herein, we report for the first time genetic analysis of a myoid hamartoma of the breast. The tumor cells had t(5;12)(p13;q14) as the only cytogenetic abnormality. The translocation led to rearrangement of the *HMGA2* gene fusing it with a sequence from chromosome band 5p13. This pattern of rearrangement is similar to what happens to *HMGA2* in other and more common connective tissue tumors, *i.e.* disruption of the *HMGA2* locus leaving intact exons 1-3 which encode the AT-hook domains separating them from the 3'-untranslated region of the gene (3'-UTR) (25, 32-34). The 3'-UTR of *HMGA2* has been shown to regulate transcription of the gene (35, 36).

Figure 1. Microscopic examination of the myoid hamartoma of the breast. A: Hematoxylin and eosin (HE)-stained section showing the area of glandular tissue next to area of smooth muscle differentiation (upper right), $\times 40$. B: HE-stained section showing smooth muscle tissue and glandular tissue, $\times 100$. C: H&E-stained section showing smooth muscle tissue and some fat cells, $\times 100$. D: Immunohistochemical examination showing expression of desmin in the smooth muscle component.

There is a plethora of data showing involvement or misexpression of the entire *HMGA2* or a truncated form of it in the development of various types of neoplasia (32, 37-40). Furthermore, mouse embryonic NIH3T3 fibroblasts are transformed *in vitro* by the expression of truncated *HMGA2* protein carrying the three DNA-binding domains (41). Overexpression of truncated *HMGA2* in human myometrial cells was shown to induce leiomyoma-like tissue formation (42). Expression of full-length as well as truncated human *HMGA2* transcripts in transgenic mice under the control of the fatty acid binding protein 4 (*Fabp4*) gene promoter, which is a differentiated adipocyte-specific promoter, resulted in the development of neoplasms including fibroadenomas of the breast and salivary gland adenomas (43). Of note, the addition of ectopic fusion sequences was not necessary for the ability of *HMGA2* to produce neoplasia (43). Recombinant *HMGA2*

protein was shown to increase the proliferative activity of chondrocytes in a dose-dependent manner in an *in vitro* system utilizing cells of porcine origin (44). Application of a synthetic peptide comprising the functional AT-hook motifs of the *HMGA2* protein onto porcine hyaline cartilage chondrocytes, grown in a monolayer cell culture, showed a growth-promoting effect similar to that of wild-type *HMGA2* protein (45).

The present study shows that myoid hamartoma of the breast may be genetically related to other types of benign tumor with *HMGA2* rearrangements such as lipomas, myolipomas, leiomyomas, chondroid hamartomas, and hamartomas of the breast (28). The findings indicate that myoid hamartomas, similarly to other hamartomas of the breast, grow from mutated mesenchymal stem cells which are capable of differentiation into stromal cells as well as to adipocytes and smooth muscle cells (29, 30).

Figure 2. Genetic examination of myoid hamartoma of the breast. A: Partial karyotype showing the der(5)t(5;12)(p13;q14), der(12)t(5;12)(p13;q14), and normal chromosomes 5 and 12. Breakpoint positions are indicated by arrows. B: Fluorescence in situ hybridization on a metaphase spread with the high mobility group AT-hook 2 (HMGA2) break-apart probe. A normal yellow signal is seen on chromosome 12, a red signal on der(12) (arrow), and a green signal on der(5) (arrow). C: HMGA2-fusion sequence obtained from the raw data after RNA sequencing using the deFuse software package. The G1G junction of HMGA2 with sequence from chromosome band 5p13 is highlighted with red. The position of the forward HMGA2-929F1 and reverse 5p13R primers are highlighted with green. D: Partial sequence chromatogram of the cDNA amplified fragment showing the junction position of HMGA2 and sequence from chromosome band 5p13 (arrow). The stop codon TAA is underlined. E: The putative protein which contains amino acid residues 1-83 of HMGA2 (accession number NP_003474.1) as well as nine amino acid residues VHSTGEKQS from the 5p13 sequence (highlighted with yellow).

Conflicts of Interest

The authors declare that they have no potential conflicts of interest in regard to this study.

Authors' Contributions

IP designed and supervised the research, performed molecular genetic experiments, bioinformatics analysis, and wrote the article. LG performed cytogenetic analysis and evaluated the FISH data. HKA performed FISH analysis and evaluated the FISH data. TDP performed the pathological examination. JL performed the pathological examination. ML-I performed the pathological examination. FM supervised the research. SH assisted with experimental design and writing of the article. All Authors read and approved the final article.

Acknowledgements

This work was supported by grants from Radiumhospitalets Legater.

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Received August 31, 2019

Revised September 23, 2019

Accepted September 26, 2019