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Monosomy 13 in Mammary Myofibroblastoma

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Abstract. *Background/Aim: Myofibroblastoma of the breast is a rare benign mesenchymal tumor whose morphology is similar to that of spindle-cell lipoma. The few hitherto genetically investigated mammary myofibroblastomas have been shown to have had loss of material from chromosome 13, changes that are also common in spindle-cell lipoma. Our aim was to add to the existing knowledge of genetic aberrations in mammary myofibroblastoma by investigating another such tumor. Materials and Methods: Cytogenetic and array comparative genome hybridization (aCGH) analyses were performed on a surgically removed mammary myofibroblastoma from a 76-year-old man. Results: Short-term cultured cells from the tumor showed the karyotype 45,XY,-13[3]/44~45,idem,add(19)(q13)[cp2]. aCGH detected loss of one entire chromosome 13 and heterozygous loss from 19q between sub-band 19q13.12 and 19qter. Conclusion: These findings add to the evidence that loss of 13q material is typical of mammary myofibroblastomas.*

Mammary myofibroblastoma is a rare benign mesenchymal tumor of the breast reported for the first time in 1987 in 11 male and 5 female adult patients as a lesion "largely composed of myofibroblasts arranged in fascicular clusters with interspersed bands of hyalinized collagen" (1). Until 2018, fewer than 90 tumors had been reported (2). In most of the publications (3-12), single cases were described adding to the evidence that these are rare tumors.

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Genetic information on mammary myofibroblastoma is available for 21 tumors: two were examined by G-banding and karyotyping (10); ten by fluorescence *in situ* hybridization (FISH) analysis using a probe specific for the forkhead box O1 (*FOXO1*) gene which maps to chromosome sub-band 13q14.11 (11, 13-15); eight using a FISH probe for the RB transcriptional corepressor 1 (*RB1* located on 13q14.2) gene (16, 17); and one tumor was examined by OncoScan as part of a copy-number variant study of 11 benign mesenchymal tumors (18). Because of the rarity of the tumor and the limited genetic information, we present here another mammary myofibroblastoma examined by banding cytogenetics and array comparative genome hybridization (aCGH).

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; 2010/1389/REK sør-øst A). Written informed consent was obtained from the patient. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

Case Report. A tumor was removed from the breast of a 76-year-old male patient. It measured 5×4×3 cm, had a solid consistency and was well demarcated from the surrounding adipose tissue (Figure 1A). Microscopically, the tumor was partly well demarcated from surrounding adipose tissue in some areas (Figure 1B) but in other areas less so (Figure 1C). The tumor cells were elongated and intermingled with hyaline fibers (Figure 1D). Loosely arranged spindle cells with indistinct cell borders were seen (Figure 1E). Mitotic figures were sparse. Necrosis was not present. No ductal structures were found within the tumor. The tumor's immunohistochemical profile was as follows: Positive markers: Cluster of differentiation 34 (CD34), CD99, and BCL2 apoptosis regulator (BCL2); negative markers: MDM2 proto-oncogene (MDM2), ETS transcription factor ERG (ERG), caldesmon 1 (CALD1), S100 calcium binding protein A1 (S100A1), melan-A (MLANA), cytokeratin AE1/AE3, CD68, KIT proto-oncogene, receptor tyrosine kinase (KIT), anoctamin 1 (ANO1), epithelial membrane antigen (EMA), mucin 4, cell surface-associated (MUC4), TLE family member 1, transcriptional corepressor (TLE1), SRY-box transcription factor 10 (SOX10), desmin (DES), and actin

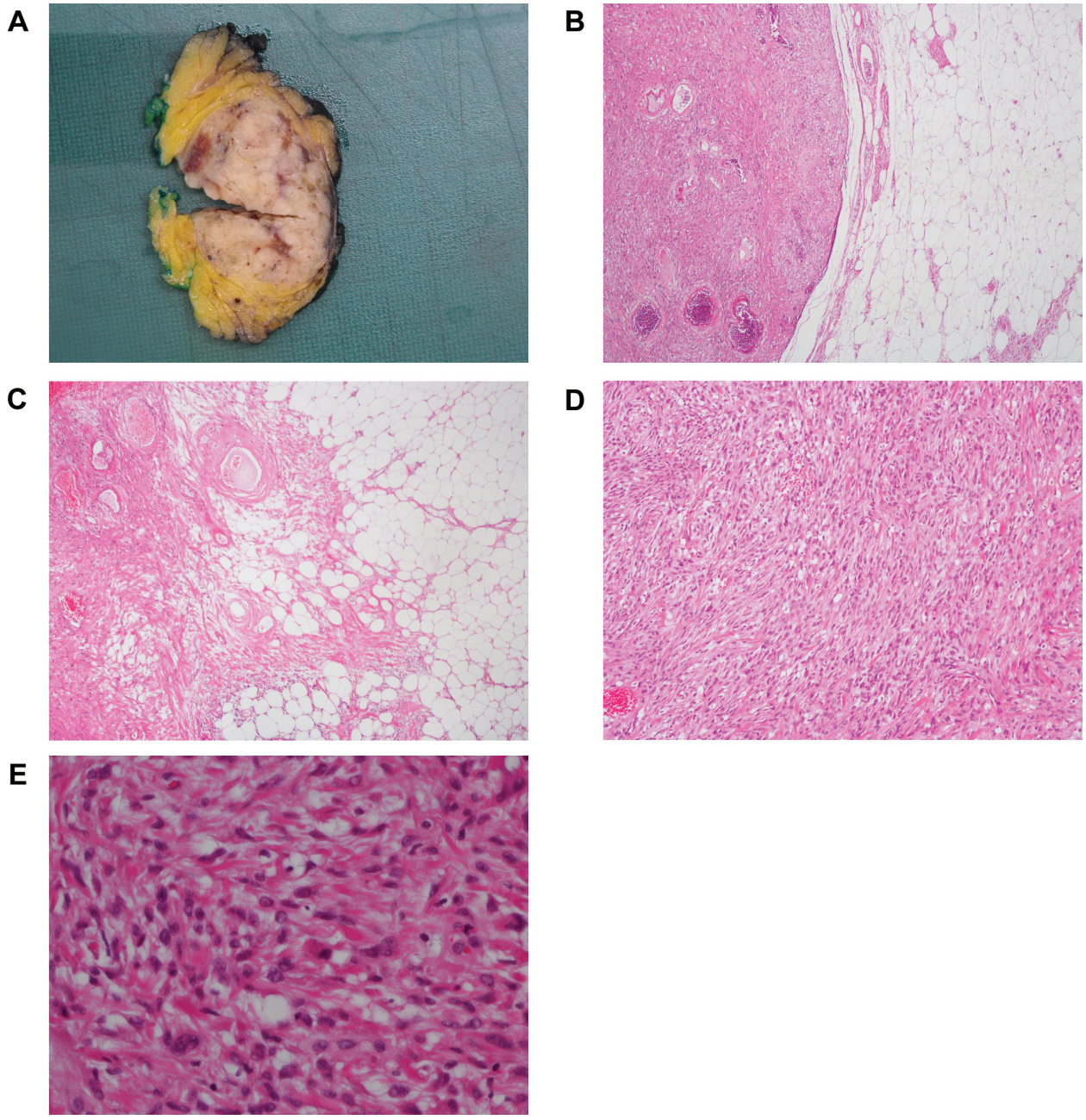

Figure 1. *Gross and microscopic images of the mammary myofibroblastoma: A: Gross view in cross section of tumor with surrounding adipose tissue. B: Tumor (left), well demarcated from the surrounding adipose tissue. 40×. C: Area in which the tumor was less well demarcated from the surrounding tissue. 40×. D: Tumor with intermingled hyaline fibers. 100×. E: Loosely arranged spindle cells with indistinct cell borders. 400×.*

alpha 2, smooth muscle (ACTA2). Signal transducer and activator of transcription 6 (STAT6) showed cytoplasmatic staining, *i.e.* the profile did not indicate any fusion of STAT6 with NGFI-A binding protein 2 (NAB2). SWI/SNF-related, matrix-associated, actin dependent regulator of chromatin, subfamily B, member 1 (SMARCB1) was retained. The diagnosis was mammary myofibroblastoma.

Chromosome banding and aCGH. Fresh tissue from a representative area of the resected tumor was used in further analyses. Cells were short-term cultured, harvested and processed for cytogenetic investigation, G-banded, and karyotyped as previously described (19). The methods for aCGH analysis have been described in detail elsewhere (20).

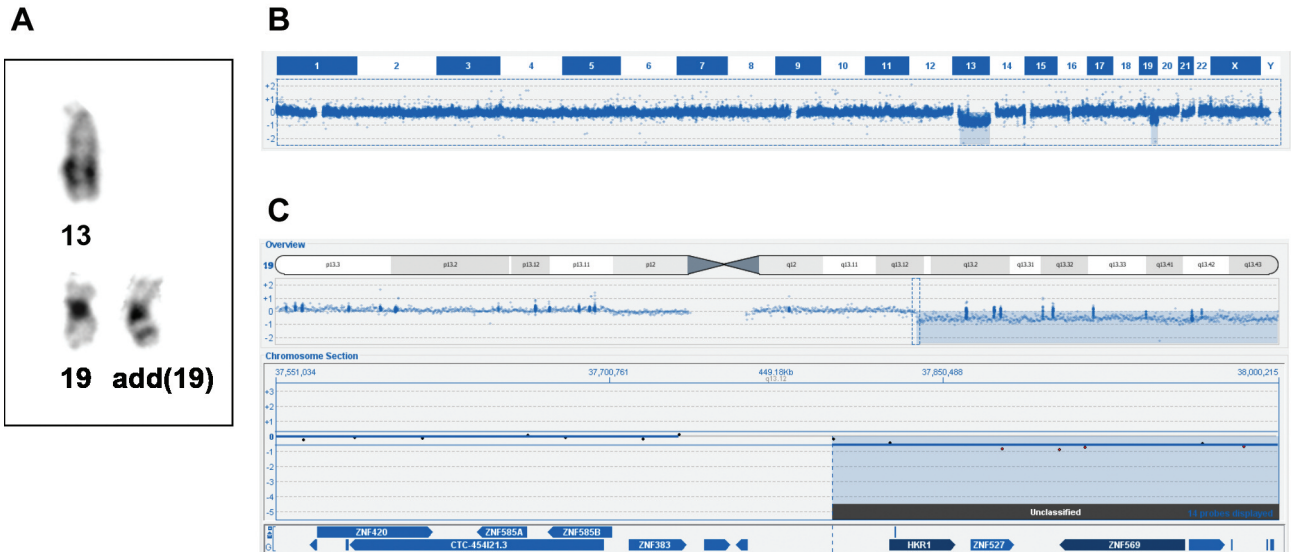

Figure 2. *Genetic analysis of the mammary myofibroblastoma: A: Partial karyotype showing monosomy 13 and add(19)(q13). B: Array comparative genome hybridization (aCGH) showing losses of chromosome 13 and material from chromosome arm 19q. C: aCGH showing loss from sub-band 19q13.12 to 19qter, probably corresponding to the additional structural rearrangement, add(19)(q13), seen by G-banding analysis.*

Results

G-Banding analysis of short-term cultured cells from the mammary myofibroblastoma showed chromosomal abnormalities corresponding to two related clones. In the first, loss of one chromosome 13 was seen. The second clone showed monosomy 13 together with a structural rearrangement in which part of the q arm of chromosome 19 had been lost (q13-qter) while additional material of unknown origin was attached to chromosome band 19q13 (Figure 2A). This corresponded to the following karyotype: 45,XY,-13[3]/44~45,idem,add(19)(q13)[cp2].

aCGH analysis detected loss of the entire chromosome 13 corresponding to the monosomy 13 seen by G-banding (Figure 2B). In addition, heterozygous loss from sub-band 19q13.12 to 19qter was found, probably corresponding to the additional structural rearrangement seen in the second clone (Figure 2C). The breakpoint of the deletion was downstream from the zinc finger protein 383 gene (*ZNF383*).

Discussion

Mammary myofibroblastomas exhibit morphological as well as (patho)genetic similarities with other benign connective tissue tumors, but perhaps especially with spindle-cell lipoma (1, 3, 6, 9, 10-18, 21-23). If we dwell on the genetics they have in common, the only two myofibroblastomas reported to date with cytogenetic aberrations both showed loss of material from chromosome 13 (10): one tumor had the karyotype 46,XY,del(13)(q?12q?32), whereas that of the second was 45,XY,add(1)(p36),-6,del(13)(q14),-der(16)t(6;16)(p11;p13)del(16)(q12). Furthermore, monoallelic deletions of the forkhead box O1 gene (*FOXO1* also known as *FKHR*, located on 13q14.11) were found in seven out of 10 mammary myofibroblastomas examined genetically with a FISH probe for *FOXO1* (11, 13-15). In other studies, monoallelic deletions of the RB transcriptional corepressor 1 (*RB1*, located on 13q14.2) gene were found in five out of nine examined mammary myofibroblastomas (16-18); eight of the cases were examined with a FISH probe for *RB1* (16, 17), whereas the ninth tumor was examined with OncoScan in a copy variant study (18). The results we present here, *i.e.*, loss of an entire chromosome 13, which would correspond to monoallelic losses of both *FOX1* and *RB1* if that had been studied, confirm the previously reported key role of -13 or other forms of loss of material from 13q in mammary myofibroblastomas.

A similar loss or deletion pattern has repeatedly been reported not only for spindle-cell/pleomorphic lipomas (19, 24, 25) but also other benign connective tissue tumors such as cellular angiofibroma (26, 27), angiolipoma (28), and pseudoangiomatous pleomorphic/spindle-cell lipoma (29). Additionally, FISH studies have demonstrated heterozygous deletions/losses of the *FOXO1*/*RB1* loci in cellular angiofibromas and extramammary and vaginal myofibroblastomas (13, 30-34).

The histopathological similarities among the above-mentioned tumors and the fact that they all often display loss of material from chromosome 13 indicates that they share the same or similar pathogenetic mechanisms. The transforming event (the loss of chromosome 13 material or some smaller preceding change) may take place in a common mesenchymal stem cell. The somewhat diverse phenotypic features of tumors sharing the same pathogenetic pathway can be accounted for by assuming that the putative tumor stem cell is already restricted in its differentiation abilities at the time of transformation.

In conclusion, our findings add to the evidence that loss of 13q material is typical of mammary myofibroblastomas.

Conflicts of Interest

The Authors declare that no potential conflicts of interest exist.

Authors' Contributions

IP designed and supervised the research, performed analyses, and wrote the article. LG performed cytogenetic analysis. ML-I performed the pathological examination. SH supervised the research and assisted with writing of the article. All Authors read and approved of the final article.

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