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Chronic Expanding Hematoma with a t(11;19)(q13;q13) Chromosomal Translocation

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Abstract. *Background/Aim: Chronic expanding hematoma is defined as a hematoma that gradually expands over 1 month or longer, is without neoplastic features on histological sections, and does not occur in the setting of coagulopathy. The pathogenetic mechanism behind its development is unknown, nor is anything known about its genetic features. Case Report: A 49-year-old man noted a tender lump close to the right femoral trochanter. Examination of a core needle biopsy showed a fibrous capsule with fibrinoid material on one side. The patient underwent surgery with removal of a cystic, encapsulated structure with central bleeding and proliferating vessels in the fibrous capsule. The reactive fibroblasts were without any sign of atypia. Genetic analyses were performed on this chronic expanding hematoma. Results: G-Banding analysis of short-term cultured cells from the chronic expanding hematoma yielded a karyotype with a single clonal chromosome abnormality: 46,XY,t(11;19)(q13;q13)[8]/46,XY[10]. RNA sequencing and examination of the sequencing data using five different programs did not identify fusion genes related to the translocation. Conclusion: The acquired translocation t(11;19)(q13;q13) suggested that chronic expanding hematoma is a neoplastic lesion. Since the translocation did not lead to any fusion genes, one can speculate that it causes deregulation of gene expression.*

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Chronic expanding hematoma is defined as a hematoma that gradually expands over a period of 1 month or longer, does not have any neoplastic feature changes on histological sections, and does not occur in the setting of coagulopathy (1). The lesion was first reported by Friedlander and Bump in 1968 (2) and was later (1980) described as an uncommon clinicopathological entity (3). Other terms used to describe the same lesion are ancient hematoma, calcific myonecrosis, and post-traumatic cyst of soft tissues (4, 5). Chronic expanding hematoma may be misdiagnosed as a malignant tumor or soft tissue (1, 6-12). The pathogenetic mechanism behind the development of chronic expanding hematoma is unknown (11) and nothing is known about its cytogenetic and molecular genetic features. We present a case of chronic expanding hematoma on which genetic analyses were performed.

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 was obtained from the patient to publication of the case details. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

Case Report

A 49-year-old man noticed a tender lump close to the right femoral trochanter which hurt under pressure. No known trauma was known at this specific site, but the patient had been a wrestler and so had experienced multiple traumas over the years. Examination of a core needle biopsy showed

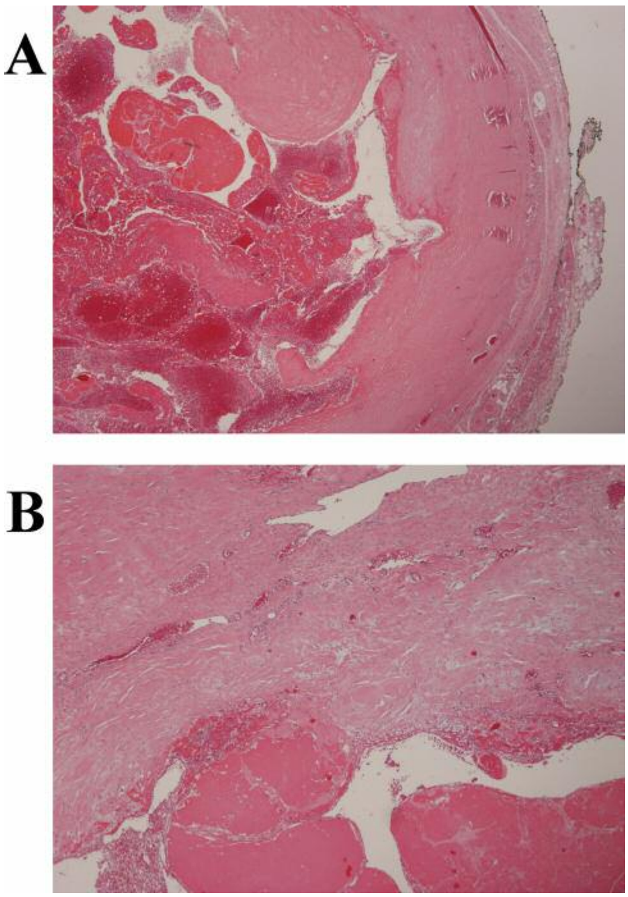

Figure 1. *Microscopic picture of the chronic expanding hematoma. Hematoxylin and eosin-stained section showing cystic lesion with a thick, fibrous capsule with reactive fibroblasts and proliferation of small vessels. In the center of the lesion there was blood. Magnification A: ×10 B: ×20*

a fibrous capsule with fibrinoid material on one side. He underwent surgery with removal of a cystic, encapsulated structure with central bleeding and proliferating vessels in the fibrous capsule. The reactive fibroblasts were without any sign of atypia (Figure 1).

Chromosome banding. Fresh tissue from the specimen was disaggregated mechanically and enzymatically with collagenase II (Worthington, Freehold, NJ, USA). The resulting cells were cultured and harvested using standard techniques (13). Chromosome 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, UK). The karyotypes were described according to the International System for Human Cytogenomic Nomenclature (14).

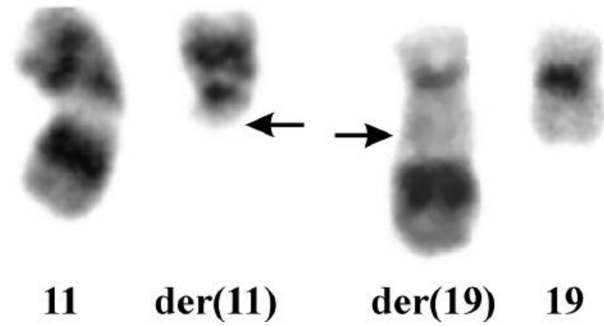

Figure 2. *Partial karyotype showing the der(11)t(11;19)(q13;q13), der(19)t(11;19)(q13;q13), and normal chromosomes 11 and 19. Breakpoint positions are indicated by arrows.*

RNA sequencing. Total RNA was extracted from frozen (–80˚C) 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, Illumina TruSeq RNA Access Library Prep kit was used (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 76 million reads were generated. The software packages FusionCatcher, deFuse, ChimeraScan, TopHat-Fusion, and FuSeq were used to find fusion transcripts (15-21).

Results of analyses. G-Banding analysis of short-term cultured cells from the chronic expanding hematoma yielded a karyotype with a single clonal chromosome abnormality: 46,XY,t(11;19)(q13;q13)[8]/46,XY[10] (Figure 2). RNA sequencing and examination of the sequencing data with five different programs did not identify any fusion genes related to the translocation (data not shown).

Discussion

To the best of our knowledge, this case of chronic expanding hematoma was the first which has been examined cytogenetically and investigated molecularly for possible generation of fusion genes. The tumor had an acquired chromosomal translocation, t(11;19)(q13;q13). This strongly suggests that chronic expanding hematoma is a neoplastic process and not an inflammatory response as was previously assumed (3, 22). However, the observed translocation did not lead to any fusion genes.

The chromosomal translocation t(11;19)(q13;q13) has also been reported as an acquired, recurrent genomic rearrangement in mesenchymal hamartoma of the liver, which is a rare benign tumor in children (23-28). Molecular studies of such tumors showed that the t(11;19)(q13;q13) of mesenchymal hamartoma was associated with deregulation of gene expression (29-31). The genomic breakpoint on chromosome 19 occurred at chromosomal sub-band 19q13.42 in a 23-kb gene-poor region (chr19:54,151,101-54173857 on human reference genome GRCh37/hg19 which was named *MHLB1* (31, 32). This *MHLB1* locus lies within the C19MC region which is the largest human microRNA gene cluster discovered to date (33). C19MC is an approximately 100-kb long cluster which consists of 46 tandemly repeated, primate-specific pre-miRNA genes that are flanked by Alu elements and embedded within a 400- to 700-nucleotide long repeated unit (chr19:54150000-54270000) (33). The C19MC region is also rich in repetitive elements and 90% of the sequence in the C19MC is comprised of Alu repeats (33). Aberrant activation of C19MC, leading to dysregulated microRNA profiles, was thus pathogenetically implicated in mesenchymal hamartoma of the liver (29-31).

On chromosome 11, the hamartoma breakpoints were located within the metastasis associated lung adenocarcinoma transcript 1 (*MALAT1*) gene on chromosomal sub-band 11q13.1 (chr11:65,264,697-65,275,032). *MALAT1* is a non-coding RNA which is ubiquitously expressed in almost all human tissues and plays a role in various cellular processes, such as alternative splicing and transcriptional and post-transcriptional regulation (34). Studies have shown that *MALAT1* is dysregulated and plays a critical role in the development and progression of various cancer types (34-37). A recurrent *MALAT1–GLI1* fusion, resulting in GLI family zinc finger 1 (*GLI1*) overexpression, was described in gastroblastomas and plexiform fibromyxomas (38, 39).

In conclusion, the finding of an acquired translocation in cells cultured from a chronic expanding hematoma strongly suggests that this is a tumor that arises through a neoplastic mechanism. The fact that the same translocation, t(11;19)(q13;q13), has also been seen repeatedly in mesenchymal hamartoma, another completely benign lesion, adds indirect evidence to this interpretation. Since the translocation did not lead to formation of any fusion genes, it is likely that dysregulation of gene expression is key to how this genomic alteration leads to neoplasia.

Conflicts of Interest

The Authors declare that no potential conflicts of interest exist.

Authors' Contributions

IP conceived the study, designed the analyses, evaluated the data, and drafted the article. LG performed cytogenetic analysis. IK performed bioinformatic analysis. IL and BB performed the pathological examination. SH supervised the research and assisted with writing of the article. All Authors read and approved the final article.

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