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Case Report Open Access

Chromothripsis in Lipoblastoma

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Abstract

Lipoblastoma is a benign tumor that often has rearrangements of the 8q11-13 region targeting the PLAG1 gene, which is involved in the process of tumourigenesis. We described a signature of chromotripsis in a thigh lipoblastoma, as first report of chromotripsis in a benign tumor.

Keywords: PLAG1; Lipomatous tumors; SNPs-array

Introduction

Lipoblastoma is a rare, benign tumor of the embryonal fat occurring mostly in children and infants less than 3 years of age, with a male predominance [1]. Most lipoblastomas arise within the soft tissue of the trunk and the extremities, but they may also occur in the head, neck, mediastinum, retroperitoneum, lungs, heart and salivary glands [2]. They commonly present as a painless mass increasing in size, otherwise its rapid growth can cause compressive symptoms [3].

Lipoblastoma often has rearrangements of the 8q11-13 region targeting the PLAG1 gene, which participates in regulation of mitogenesis, proliferation and apoptosis and is involved in the process of tumourigenesis [4,5]. Two oncogenic mechanisms have been proposed. On one side, the aforementioned rearrangements cause promoter swapping, in which the PLAG1 promoter element is replaced by an active one, and ultimately causes upregulation of the PLAG1 transcription factor [6]. In some cases, however, a polysomy for chromosome 8, involving PLAG1 copy number gain, has been described [6,7].

We present a signature of chromotripsis on chromosome 8 in a thigh lipoblastoma.

Material and Methods

After approval by the Institutional Ethical Commitee, the medical record of the patient was analyzed and DNA extracted from the lipoblastoma was screened using HumanCytoSNP-12 Bead Chip (Illumina Inc., San Diego, CA, USA) which contains nearly 300,000 genetic markers. Single nucleotide polymorphism (SNP) copy number (log R ratio) and B-allele frequency were assessed using the software Genome Studio 2011.1 (CNV partition 3.2.0) (Illumina). Copy number variant (CNV) regions overlapping with Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation) CNVs were not considered. Furthermore, all CNVs with ≤20 contributing SNPs were excluded.

Results

The 5-year-old boy was referred to our hospital with a growing right thigh mass without any other accompanying symptoms and no history of trauma. On physical examination, a 1.5 cm × 2 cm solid, painless mass with normal overlying skin was palpated. Results of laboratory tests tumor markers (α-fetoprotein, serum β human chorionic gonadotropin, carcinoembryonic antigen and urinary catecholamine metabolites) were within normal limits. An ultrasound color Doppler detected a heterogeneous mass with a hyperechoic component inside the quadriceps femoris muscle. An excisional biopsy of the mass was performed to make a definitive diagnosis. Histopathological examination revealed a lipoblastoma, with a characteristic lobular architecture and fibrous septa between nodules of adipose tissue in various stages of maturation.

SNPs-Array analysis revealed many CNVs involving chromosome 8. Six CNVs trisomy and one tetrasomy were observed (Figure 1 and Table 1). The breaking points of a CNV (46,942,842-57,100,149) fell within the PLAG1 gene (chr8:57,073,462-57,123,858 OMIM 603026), resulting in a breakage of the gene. One of the PLAG1 isoforms was included in the duplicated segment, resulting in its overexpression. All other chromosomes were normally expressed.

Discussion

Lipoblastomas are fatty tumors primarily affecting children younger than 3 years of age and occurring mostly in arms and legs, but also in the head, neck, trunk, mediastinum and retroperitoneum. Although lipoblastomas do not metastasize, they can recur locally after incomplete excision [8].

Chromosomal rearrangements involving the 8q11-13 region have been reported in lipoblastoma, targeting the PLAG1 oncogene, which encodes a zinc finger transcription factor primarily expressed in fetal tissue and only at very low levels postnatal [9]. PLAG1 gene is involved in mitogenesis, proliferation, IGF-2 up-regulation, and apoptosis. It regulates the development of the central nervous system and the neuroendocrine and olfactory cells [2]. It has been suggested that the oncogenic mechanism in lipoblastoma is based on PLAG1 oncogene upregulation either because of rearrangements on the long arm of chromosome 8 or because of gain of chromosome 8 extra copies with or without PLAG1 rearrangements.

Recent studies have revealed that many tumor cells harbor chromosomes bearing tens to hundreds of clustered genome rearrangements, which occurred in a one-step cataclysmic process termed chromothripsis [10]. This is a widespread phenomenon

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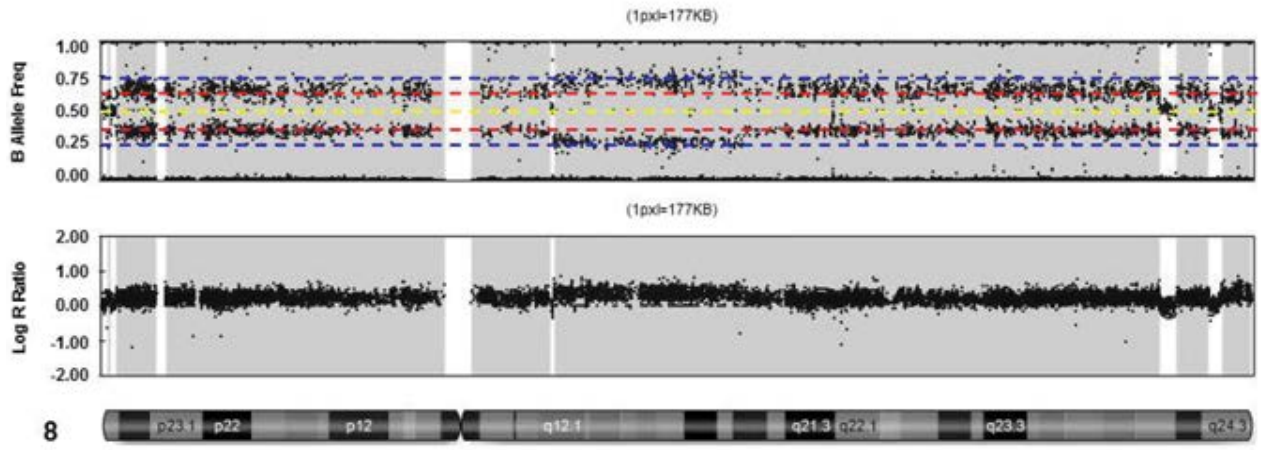

Figure 1: SNP array analysis of chromosome 8. The white lines match with CNV=2. Yellow dashed line for CNV=2 (disomy). Red dashed lines for CNV=3 (trisomy). Blue dashed lines for CNV=4 (tetrasomy).

From	To	CNV	Length (bp)
176,818	673,561	2	496743
706,008	1,165,148	3	459140
1,174,325	1,818,575	2	644250
1,832,844	43,646,413	3	31813569
Centromere			
46,942,842	57,100,149	3	10157307
57,135,889	57,461,226	2	325337
57,479,269	81,709,470	4	24230201
81,771,461	134,592,424	3	52820963
134,598,104	136,735,506	2	2137402
136,738,670	140,863,075	3	4124405
140,869,942	142,437,352	2	1567410
142,443,023	146,293,086	3	3850063

Table 1: CNVs on chromosome 8. CNV=2: disomy; CNV=3: trisomy; CNV=4: tetrasomy. Length is expressed in base pairs (bp).

described in 2% to 3% of cancers, including bone cancer, lung cancer, pediatric medulloblastoma, neuroblastoma, colorectal cancer, melanoma, and hematological malignancies. Similar complex rearrangements were also found in patients with congenital disease [11].

We recognized a signature of chromotripsis in our case. All the rearrangements were localized on chromosomal arm 8 with copy number changes and pronounced clustering of breakpoints. The overexpression of one of the PLAG1 isoforms supported the hypothesis that up regulation of PLAG1 oncogene is involved in the oncogenic process. To the best of our knowledge this is the first report of chromotripsis in a benign tumor. Analysis of additional cases of lipoblastoma may further clarify the existence of one-off cellular catastrophe as oncogenic mechanism in this benign tumor.

FP conceived the study and analyzed data. VC and LC carried out experiments. VP conceived experiments and analyzed data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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