

# Anisometric Cell/Dysplastic Lipomas in a Retinoblastoma Survivor: Report of a Case with Review of the Literature

International Journal of Surgical Pathology  
2023, Vol. 31(8) 1632–1637  
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DOI: 10.1177/10668969231157779  
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## Abstract

Different authors have recently described a subtype of lipoma characterized by variation of adipocyte size, single cell fat necrosis, and a subset with minimal to mild nuclear atypia, and termed these as anisometric cell/dysplastic lipoma (AC/DL). These lipomas follow a benign course and rarely recur. In 3 examples, AC/DL has occurred in patients with childhood retinoblastoma (RB). We report another such example where multiple AC/DL occurred in the neck and back of a 30-year-old male who had germline *RB1* gene deletion and bilateral RB in infancy. On excision, all tumors histologically showed similar morphology of adipocyte anisometry, focal single cell necrosis with surrounding binucleated or multinucleated histiocytes, hyperchromatic and minimally atypical lipocyte nuclei, vacuolated *Lockhern* change, rare foci of fibromyxoid change, occasional mononuclear cell clusters around capillaries, and loss of RB1 immunostaining. Unequivocal atypical cells, lipoblasts, floret-nucleated or multinucleated giant cells were absent. Molecular analysis of tumor cells showed monoallelic *RB1* gene loss without amplification of *MDM2* and *CDK4* genes. Short-term follow up did not show tumor recurrence. AC/DLs in RB survivors are characterized by multiplicity, unifying histology, and benign course. Their biology appears distinct from ordinary lipomas, spindle cell lipomas, and atypical lipomatous tumors.

## Keywords

lipoma, dysplastic lipoma, RB1, MDM2, retinoblastoma

## Introduction

In 2015, Dr Evans described 13 cases of a unique lipomatous tumor and labeled it as “anisometric cell lipoma.”<sup>1</sup> This was followed by additional comprehensive descriptions of a number of cases by Agaimy<sup>2</sup> and Michal et al.<sup>3</sup> The common features of these benign lipomatous tumors were presence of significant size variation in tumor lipocytes, minimal to mild nuclear atypia, and foci of necrotic single adipocytes—ultimately termed as “dysplastic” lipoma. Interestingly a clinical association with retinoblastoma in infancy was reported in rare instances.<sup>1,3,4</sup> This association was again documented recently by den Bakker et al.<sup>5</sup> We report another such case of an anisometric cell/dysplastic lipoma (AC/DL) in a retinoblastoma survivor. We present, to the best of our knowledge, the fourth case in the literature of this extremely rare association and review the previously documented examples.

## Case Report

A 30-year-old male presented with complaint of soft tissue masses located on the posterior back and neck, noticed 6 months ago due to continued growth and mild pain. His medical history was significant for bilateral retinoblastoma

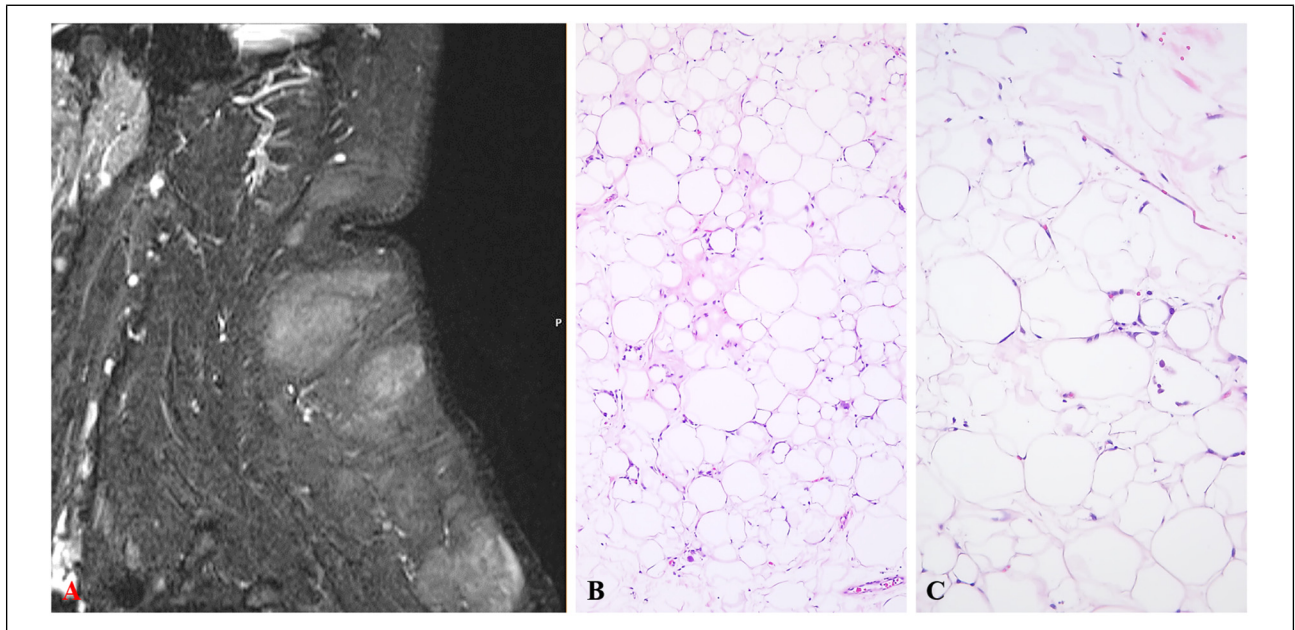
diagnosed at 2 weeks of life and treated with orbital radiation and cryotherapy, and embryonal rhabdomyosarcoma of the nasopharynx at 4 years of age, treated with surgical resection and neoadjuvant chemoradiation therapy. A detailed family history revealed cancer history in several relatives, including grandparents, but not in biological parents. Germline (saliva) testing showed a heterozygous pathogenic *RBI* exon 11 variant c.1072C>T (p.Arg358\*) gene sequence, encoding a premature translational stop codon expected to result in an absent or disrupted protein (loss-of-function mutation).

He remained symptom-free until his most recent presentation. Physical examination showed dense, mobile masses on the upper back and posterior neck. Magnetic resonance imaging showed multiple ill-defined subcutaneous lesions demonstrating T1 hyperintensity and postcontrast enhancement with features suggestive of fat components

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**Figure 1.** (A) MRI showing multiple subcutaneous masses in the neck and back with postcontrast enhancement. (B) Low-power and intermediate-power showing striking variation in adipocyte size with a slight fibrous stroma in the center. (C) Minimal to mild hyperchromasia of the adipocyte nuclei is present with single cell fat necrosis (H&E). Original magnification (H&E) A:  $\times 50$ , B:  $\times 100$ . Abbreviations: H&E, hematoxylin and eosin; MRI, magnetic resonance imaging.

(Figure 1A). The largest lesion was present in the cervical neck subcutaneous tissue and measured 6 cm. Excision was performed of multiple neck and back tumors (6 nodules) with no immediate or late postoperative sequelae. A skin cyst from the right lower back was also excised.

Grossly, multiple lobulated lesions with a translucent, thin capsule were examined. The largest excised lesion measured 5 cm. Histologically, all tumors were composed of adipocytes with striking size variation appreciable at low power (Figure 1B-C). On high power, the adipocytes showed focal single cell necrosis with binucleated or multinucleated histiocytes surrounding fat vacuoles, hyperchromatic and occasionally enlarged lipocyte nuclei, vacuolated *Lockhern* change, rare foci of fibromyxoid change, and occasional blood vessels with surrounding mononuclear population (Figure 2A-E). No unequivocal atypical stromal cells, lipoblasts, floret-nucleated or multinucleated giant cells were identified. By immunohistochemistry (IHC), P53 (clone DO-7; 1:60; Dako) was positive in  $\sim 5\%$  of adipocytic nuclei (Figure 2F). Retinoblastoma-1 antigen (RB1, clone 1F-8; 1:50; Thermo Fisher Scientific) showed loss of nuclear staining in nearly all adipocytes with retained expression in mononuclear and endothelial cells (Figure 3A). Fluorescence in situ hybridization (FISH) performed on formalin-fixed paraffin embedded tissue for *RB1* (RB1/13q14; Vysis LSI 13, Abbott Laboratories) showed  $>50\%$  cells with monoallelic loss in probe signal, confirming retained heterozygosity of *RB1* (Figure 3B). FISH for mouse double minute 2 homolog

gene (*MDM2*/12q15; Kretech Repeat-Free Poseidon, Leica Biosystems) and cyclin dependent kinase 4 gene (*CDK4*/12q13; Kretech RF Poseidon, Leica Biosystems) did not show gene amplification (Figure 3C).

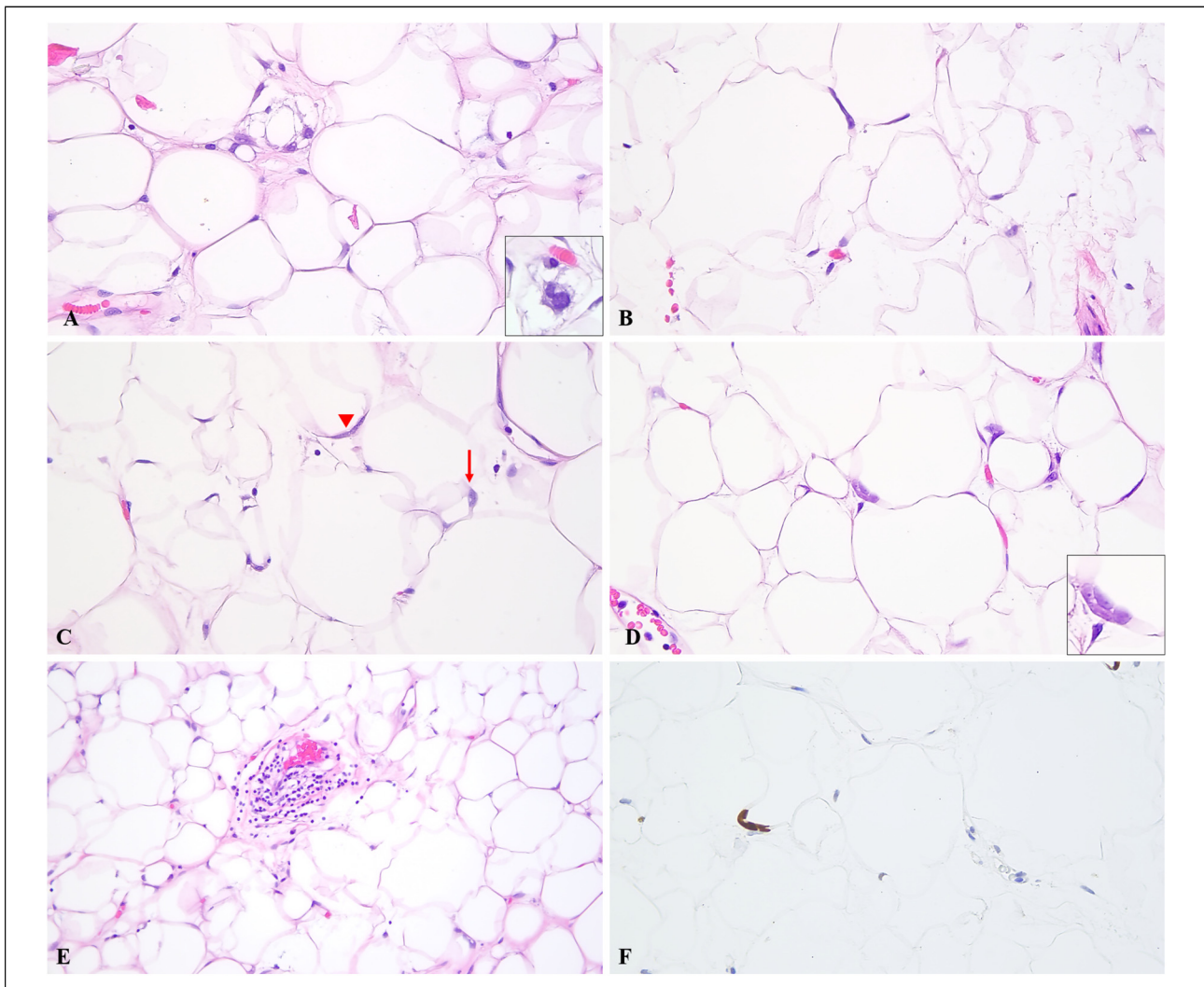
The patient was scheduled for a yearly follow up. No recurrence was reported on the short 3-month interval.

We searched our hospital database from 2005 to 2022 for additional fatty tumors reported in retinoblastoma survivors. We came across only one other case of an atypical lipomatous tumor arising in the orbit (radiation field); no benign adipocytic tumors were reported during this period to incorporate in this study.

## Discussion

*RB1* is located on chromosome 13q14.2 and encodes a tumor suppressor protein that controls the cell cycle. Absence of *RB1* results in unchecked cell proliferation. Germline *RB1* deletions are associated with bilateral retinoblastoma. Incidence of lipomas is higher in survivors of hereditary retinoblastoma (3% to 18%) as opposed to sporadic cases ( $<1\%$ ), albeit it is still rare.<sup>6-8</sup> In our database search for fatty tumors in retinoblastoma survivors, we came across one other case of an atypical lipomatous tumor arising in the orbit (radiation field), which underscores the fact that adipocytic tumors are indeed rare events in retinoblastoma patients.

Somatic *RB1* deletions genetically underpin a group of soft tissue tumors that contain fat as an integral



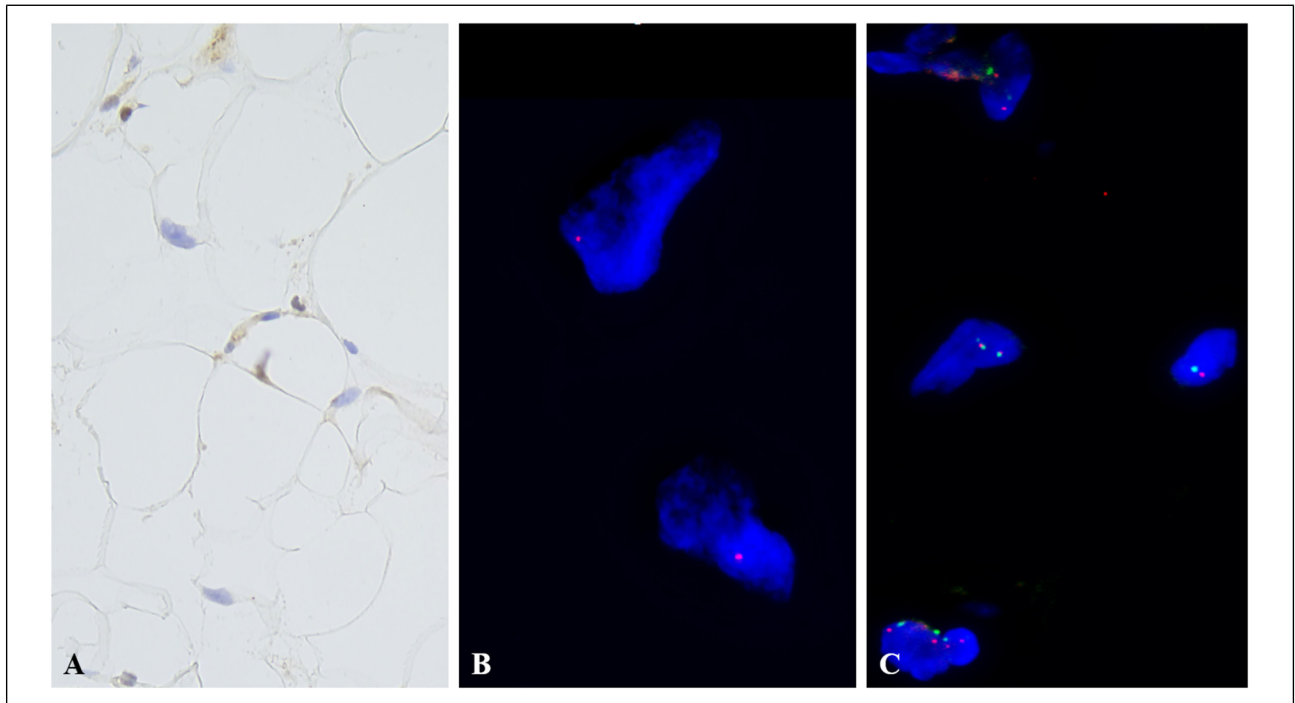
**Figure 2.** (A) Single cell fat necrosis with a binucleated histiocyte (inset). (B) Minimal atypia of adipocyte nuclei characterized by nuclear hyperchromasia. (C) Binucleation of adipocyte nucleus (arrowhead) with focal nuclear vacuolation (arrow). (D) In addition to hyperchromasia, rare adipocytes showed multinucleation (inset). (E) Background capillaries with a cuff of mononuclear cells and surrounding adipocytic anisometry (H&E). (F) P53 immunohistochemical stain showing rare nuclear staining (~5% of adipocytes). Original magnification: A–D, F:  $\times 400$ , E:  $\times 200$ . Abbreviation: H&E, hematoxylin and eosin.

component.<sup>9</sup> This group includes spindle cell/pleomorphic lipoma, atypical spindle cell/pleomorphic lipomatous tumor, pleomorphic liposarcoma, myofibroblastoma, cellular angiofibroma, and acral fibromyxoma.<sup>9</sup> These tumors have not been described in association with retinoblastoma so far. In addition, deletions of the *RBI* gene locus (13q) were also noted in 6 of 87 ordinary lipomas.<sup>10</sup>

In Evans' description of 14 anisometric-cell lipomas (characterized by adipocyte anisometry, single cell foci of fat necrosis, and slight to minimal nuclear atypia), one occurred in a patient with childhood history of bilateral retinoblastoma.<sup>1</sup> Subsequently, Michal et al (in their cohort of 66 cases) and den Bakker et al reported 2 more tumors in patients with bilateral retinoblastoma (summarized in Table 1)—both authors adopted the term “dysplastic”

lipoma for the tumors that showed increased nuclear size, coarse chromatin, and frequent intranuclear vacuoles.<sup>3,5</sup> It is presumed that dysplastic lipomas may harbor *TP53* mutations<sup>5</sup>; we did not perform genetic testing for *TP53* mutation and P53 IHC was equivocal in our case. In our practice, we have adhered to the combined nomenclature of “anisometric cell/dysplastic lipoma” since the distinction is unclear at this time. We however note the suggestions made by den Bakker.<sup>5</sup>

Overlapping features between AC/DL and spindle cell lipoma, such as predilection for the shoulder and back, histological features, and underlying genetic aberrations begs the question: are both these entities the same? As Agaimy pointed out for anisometric cell lipoma (not dysplastic lipoma), these can be considered a “fat-only” spindle cell



**Figure 3.** (A) RB1 immunohistochemistry showing loss of nuclear staining in the adipocyte nuclei ( $\times 400$ ). (B) FISH for RB1 shows monoallelic signal indicative of heterozygous RB1 gene deletion. (C) FISH for MDM2 showing nonamplified normal signals. Abbreviation: FISH, fluorescence in situ hybridization; RB, retinoblastoma.

lipoma,<sup>2</sup> although we agree that consistent paucity or absence of fibromyxoid stroma in AC/DL argues against this. In addition, spindle cell lipomas on the pleomorphic spectrum show much more profound atypia than seen in the minimally atypical cells of AC/DL (and hence the earlier term of lipomas with minimal atypia by Evans).<sup>4</sup> These interesting points were also communicated between Creytens and den Bakker, separately.<sup>11,12</sup> Creytens et al also commented that at least some dysplastic lipomas could represent “fat-rich” or “spindle cell-poor” variants of atypical spindle cell lipomatous tumor, another recognized tumor with *RB1* deletion.<sup>13</sup> We recommend separation of AC/DL from spindle cell lipoma to improve recognition by pathologists and thereby provide additional follow-up accumulation.

In our review of the literature, all previously reported retinoblastoma-associated AC/DL showed multiplicity. In contrast, among all 83 patients reported to have AC/DL outside the history of retinoblastoma,<sup>1–3</sup> 11 (13%) showed more than 1 fatty tumors; 4 (5%) of these 83 patients were confirmed to be multiple AC/DL. In the remaining, either the additional fatty tumors were not available for review or turned out to be ordinary lipomas. Although, the number is too small to draw any conclusion, it does suggest that germline *RB1* deletion predisposes to multiple AC/DL. Additional studies of larger cohorts are needed at this time for insight to the underlying biology.

Two histological differentials that warrant mention are fat necrosis and atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL). The single cell lipocyte necrosis encountered in AC/DL is distinctly different than that seen in traumatized ordinary lipomas. For example, binucleated or multinucleated histiocytes surround a necrotic fat cell without damage to any adjacent foci. Further, the reactive fibrosis is limited (or even absent) and does not form a discrete area that is conventionally seen in fat necrosis. We hypothesize that *RB1*-mediated cell cycle dysregulation leads to adipocytic dysplasia with spontaneous apoptosis<sup>14</sup> leading to anisometry as well as the single cell necrosis. Further studies are needed to determine this.

The atypical cells seen in ALT/WDL tend to be present in traversing fibrous septae that courses near a blood vessel. In contrast, the minimally atypical nucleus in AC/DL is always noted in a fat cell and not in a fibrous band. MDM2 IHC is a useful screening tool to distinguish between the 2, however a small subset can show weak (1+ or 2+) staining<sup>3</sup>; *MDM2* amplification is consistently negative by FISH.<sup>3</sup>

Histopathological descriptions of lipomas in retinoblastoma survivors are limited in the literature and as speculated before,<sup>2</sup> many reported such associations may very well represent AC/DL. These tumors tend to present as multiple subcutaneous masses usually as the survivor approaches their third decade of life. Adipocyte anisometry

**Table 1.** Clinical, Pathological, and Molecular Genetic Features of All Reported AC/DL in Retinoblastoma Survivors.

Author	Age/sex	Location/size of lipoma(s)	Histological and IHC features	Molecular features	Treatment/recurrence
Evans <sup>1</sup>	36 years / male	Left scrotum/15 cm; right scrotum/11 cm; left inguinal/10 cm; right buttock/7.1 cm	Lipocyte anisometry, single cell fat necrosis, slightly enlarged, and hyperchromatic adipocyte nuclei, focal intranuclear vacuolation; IHC details N/A	Negative for <i>CPM</i> gene amplification	Multiple lipomas, excisions since age 24 years / NA
Michalet al <sup>3</sup>	34 years / male	Neck/trunk, upper arm, bilateral scrotal area/all less than 9 cm	Lipocyte anisometry, single cell fat necrosis, other features not specified; negative <i>MDM2</i> and <i>CDK4</i> IHC; <i>RB1</i> IHC partially lost	Negative for <i>MDM2</i> amplification by FISH	Multiple excisions since 26 years / NER
den Bakker et al <sup>5</sup>	42 years / female	Left shoulder, right neck, left neck, right upper arm, right shoulder/1-2 cm, each	Lipocyte anisometry, single cell fat necrosis in 5 of 6 tumors; 1 of 5 showed dispersed atypical adipocytes, with enlarged, irregular, lobulated or angulated, and variably hyperchromatic nuclei; 1 of 6 showed features of angiolipoma; <i>RB1</i> IHC lost in all, <i>P53</i> IHC positive in 90% nuclei in 1 of 6 tumors, <i>p16</i> IHC negative in all	<i>RB1</i> FISH showed polysomy with loss in 1 of 6, possible loss in 1 of 6, and no loss in 4 of 6; <i>MDM2</i> FISH showed polysomy in 2 of 6 and no amplification in 4 of 6; <i>RB1</i> SNP array showed LOH (4 of 6) and RH (2 of 6); loss of wild-type gene by Sanger sequencing in 4 of 6; <i>TP53</i> mutation [c.1009C > T (p.R337C)] by NGS in case with <i>P53</i> positive IHC; no fusions on NGS fusion panel	Excisions/NER (on limited follow up)
Current case	30 years / male	Right back and neck, multiple (6 tumors)/5 cm, size of the largest	Lipocyte anisometry, single cell fat necrosis with binucleated histiocytes, hyperchromatic, and occasionally enlarged lipocyte nuclei, vacuolated fat cells; <i>RB1</i> IHC lost in fat cell nuclei, <i>P53</i> IHC positive in ~5%	<i>RB1</i> FISH showed monoallelic loss in >50% cells nuclei, <i>MDM2</i> and <i>CDK4</i> negative for gene amplification	Excisions/NER (short follow up)

Abbreviations: AC/DL, anisometric cell/dysplastic lipoma; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; LOH, loss of heterozygosity; NA, not available; NER, no evidence of recurrence; NGS, next-generation sequencing; RB, retinoblastoma; RH, retained heterozygosity; SNP, single nucleotide polymorphism.

and single cell fat necrosis appear to be unifying features, with minimal atypia, lipocyte binucleation, and hyperchromasia seen in a subset of cases. Although these tumors may apparently be on a spectrum with spindle cell lipomas, the multicentricity, especially in germline *RB* mutations provides a counterargument. The histological features can be alarming and therefore ancillary techniques to detect *MDM2* amplification are an invaluable adjunct. Larger studies of these rare tumors are needed to fully understand the biology, as well as to establish if these are different from AC/DL presenting outside the history of germline *RB1* mutation.

### Author Contributions

FM and KC were involved in acquisition, analysis, interpretation of data, and manuscript drafting and editing.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.


### Trial Registration

Not applicable, because this article does not contain any clinical trials.

## Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

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