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Anisometric cell lipoma: Insight from a case series and review of the literature on adipocytic neoplasms in survivors of retinoblastoma suggest a role for RB1 loss and possible relationship to fat-predominant ("fat-only") spindle cell lipoma

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ABSTRACT

The term "anisometric cell lipoma" (ACL) has been proposed recently by Evans for a lipoma variant characterized by striking variation in size and shape of adipocytes but little or no cytological atypia. One patient with multiple ACL had a history of retinoblastoma. The current study analyzed six patients with ACL (4 males and two females aged 34 to 87 years; median, 58); all seen in consultation. Five patients presented with solitary and one with multiple subcutaneous masses measuring 5 to 9 cm (median, 7.5 cm). Affected sites were upper arm (3), shoulder (2), neck (1), trunk (1) and chest wall (1). Surgical excision was the treatment in all cases. No recurrence was recorded at last follow-up (1–17 months). Submitted diagnoses were atypical lipomatous tumor (n = 3), lipoma with regressive changes (n = 1) and unclassified lipomatous neoplasm (n = 2). In all cases, the striking variation in size of adipocytes was mentioned as the most or sole worrisome feature justifying external consultation. Histology was similar in all cases. All fulfilled the features reported by Evans as stated above and lacked any conventional spindle cell lipoma-like areas. Multi-vacuolated (lipoblast-like) cells were seen in three cases. MDM2/CDK4 were negative by immunohistochemistry and MDM2 amplification was absent by FISH in all cases. RB1 immunoexpression was lost in 5/5 cases. *Rb1* FISH analysis revealed copy number aberrations in 3 of 4 cases (heterozygous deletions in two cases and homozygous deletion in one). In conclusion, ACL shares similar clinicopathological, demographic and molecular features as spindle cell lipoma suggesting related diseases. In the light of the available literature on adipocytic neoplasms in retinoblastoma survivors (> 30 patients with multiple lipomas following retinoblastoma reported), it is probably that retinoblastoma-associated lipomas belong to the ACL category. Thus, it seems that Somatic RB1 loss probably drives sporadic ACL in a comparable way to post-retinoblastoma lipomas which were shown to be driven by LOH of the *RB1* wild-type allele.

1. Introduction

Spindle cell lipoma is an uncommon benign lipoma variant that represents < 2% of adipocytic neoplasms [1]. It occurs mainly as a well circumscribed subcutaneous lesion with a striking predilection for the posterior neck, back and shoulder area of middle-aged and elderly men [1,2]. Since original description by Enzinger and Harvey in 1975 [1], several case series have been published delineating low-fat/fat-poor and pseudoangiomatous variants [2-4]. Moreover, loss of the retinoblastoma antigen 1 (RB1) located at chromosome 13q14 has been recognized as the driver of tumorigenesis in spindle cell lipoma making RB1 immunohistochemistry (IHC) a valuable adjunct tool in evaluation of difficult-to-classify and variant lesions [5].

In 2015, Evans presented a series of subcutaneous fatty tumors exhibiting notable variation in the size of fat cells but little or no atypia [6]. The tumors showed significant predilection for adult males (12/13) with a median age of 57 years and half of them occurred on the back and neck. One patient with multiple such tumors had a history of childhood retinoblastoma [6]. In a very recent report, Evans coined the term "anisometric cell lipoma" (ACL) for these lesions to draw attention to the striking variation in size of adipocytes as their hallmark [7].

However, the pathogenesis of these lesions and their relationship to other well defined adipocytic neoplasms, in particular to spindle cell lipoma, remain unclear. The aim of the current study is to analyze the

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clinicopathological features of 6 new cases and to address the hypothesis of RB1 loss as possible molecular pathogenesis in light of the previously reported patient with a history of retinoblastoma and multiple adult-onset ACLs.

2. Material and methods

Cases encoded by the descriptive term "*minimally atypical lipomatous tumor*" were retrieved from the author's consultation files (all were submitted during the last two years following the presentation by Dr. Evans at the Annual Meeting of the United State & Canadian Academy of Pathology (USCAP) in Boston, 2015). Immunohistochemistry (IHC) was performed on 3–4-μm sections cut from paraffin blocks using a fully automated system ("Benchmark XT System", Ventana Medical Systems Inc., Tucson, Arizona, USA) and the following antibodies: CD34 (clone BI-3C5, 1:200, Zytomed), retinoblastoma antigen 1 (Rb1, clone G3-245, 1:200, BD-Pharmingen), MDM2 (clone IF1, 1:50, CalBiochem) and CDK4 (clone DCS-156, 1:100, Zytomed). Protein S-100 (polyclonal, 1:2500, Dako) was used to highlight the presence of lipoblast-like or multivacuolated cells.

To detect copy number alterations of the *Rb1* gene locus, FISH was performed on 1 to 2 μm thick sections cut from formalin-fixed paraffin-embedded tissue blocks using the ZytoLight SPEC *RB1/13q12* Dual Color Probe (ZytoVision, Bremerhaven, Germany) with standard protocols according to the manufacturer's instructions as described previously [8]. The SPEC RB1/13q12 Dual Color Probe is a mixture of an orange fluorochrome direct labeled SPEC RB1 probe specific for the *Rb1* gene at 13q14.2 and a green fluorochrome direct labeled SPEC 13q12 probe specific for the 13q12.11 as supplied by the manufacturer.

3. Results

3.1. Clinical features

Six cases were retrieved. Affected were 4 males and two females with an age range of 34 to 87 years (median, 58). Five patients presented with a solitary subcutaneous mass. One patient had multiple subcutaneous tumors at different sites (Table 1). The tumor sites were upper arm (3), shoulder (2), neck (1), trunk (1) and chest wall (1). The size of the lesions ranged from 5 to 9 cm (median, 7.5 cm). Initial treatment was surgical excision in all cases, with some cases being submitted as multiple fatty fragments. Clinical data on other associated diseases was not available. At the time of preparing this study (1 to 17 months), no recurrence has been recorded.

3.2. Pathological findings

Submitted diagnoses were atypical lipomatous tumor (n = 3), lipoma with regressive changes (n = 1) and unclassified lipomatous neoplasm (n = 2). In all cases, the striking variation in size of adipocytes was noticed by the submitting pathologists and was stated as the most or sole worrisome feature justifying external consultation. Gross description was not different from that of conventional lipomas.

Histological examination showed almost identical morphology in all cases. All fulfilled the features reported by Evans with striking variability in the size of the adipocytes, minimal or no nuclear atypia and minimal or no fibrous areas (Fig. 1A–C). Variable features of regressive changes in the form of scattered large histiocytes occasionally with ring-like arrangement surrounding single fat vacuoles were seen in almost all cases (Fig. 1B). There were no hyperchromatic atypical stromal cells, multinucleated giant cells, floret-like cells or atypical lipoblasts nor were there any prominent or irregular fibrous septa (Fig. 1C). A spindle cell component as seen in conventional spindle cell lipoma was lacking. Lipoblast-like cells with variable cytoplasmic vacuoles were seen in three cases. However, these cells frequently lacked identifiable nuclei and featured minute grape-like vacuoles that were either arranged at the cell periphery in a chicken wire-like pattern (Fig. 1D) or formed aggregates within otherwise empty macrovesicular adipocytes (Fig. 1E). Focal mononuclear inflammatory cells admixed with macrophages were seen surrounding single adipocytes in most of cases and were prominent in one case (Fig. 1F). The nuclei of the adipocytes lacked any significant atypia but nuclear vacuoles ("*Lochkern*" phenomena) were easily identified (Fig. 1F). By IHC, weak MDM2 or CDK4 reactivity was observed in a few scattered macrophages but the neoplastic cells lacked either. FISH analysis using MDM2 dual color probe was negative for MDM2 amplification in all 6 cases. Scattered stroma cell were immunoreactive with CD34. The multi-vacuolated cells described above were highlighted using protein S100 IHC (Fig. 2A). In addition, RB1 immunostaining showed variable loss of staining in the adipocytic cell nuclei in 5/5 cases (Fig. 2B) and in the few scattered stromal cells (Fig. 2C). The stromal histiocytes and endothelial cells in the background were strongly positive for RB1 (internal control).

FISH analysis using the ZytoLight SPEC *RB1/13q12* Dual Color Probe was successful in four tumors from 4 patients. *Rb1* copy number abnormalities were detected in 3 cases (Fig. 2D). Two tumors showed heterozygous deletions (with variable proportions of tumor cells showing in addition loss of centromere 13q12 indicating monosomy at this gene region) and one tumor showed a homozygous deletion.

4. Discussion

Although the original report on spindle cell lipoma has mentioned the presence of lesions on both extreme ends of its morphological spectrum, to date only low-fat/fat-poor but not fat-predominant (fat-only) variants of spindle cell lipoma have been well characterized [4]. Possibly this is because of lacking reproducible diagnostic features that would permit separation of a fat-predominant ("fat-only") spindle cell lipoma from ordinary lipoma and also due to the benign nature of both lesions with little clinical impact of this separation. In a recent study,

Table 1
Clinicopathological and molecular features of anisometric cell lipoma (n = 6).

No.	Age/sex	Site	Size cm	No. of tumors	Treatment	Lipoblast-like cells	MDM2 FISH	RB1 IHC	RB1 FISH
1	48 M	Chest wall	8	1	Excision	−	−	Loss	NR
2	87 F	Right upper arm	7	1	Excision	+	−	NR	NR
3	34 M	Neck, trunk & upper arm	~9	Multiple	Excisons since age 26	+	−	Loss	No abnormalities detected
4	55 M	Left upper arm	> 6	1	Excision, fragmented	−	−	Loss	Heterozygous deletion (13q monosomy in some cells)
5	62 F	Right shoulder	9	1	Excision	−	−	Loss	Heterozygous deletion
6	68 M	Left shoulder	5	1	Excision, fragmented	+	−	Loss	Homozygous deletion

NR, nor results due to poor signal quality.