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REVIEW

Lipoblastoma Arising in the Head and Neck: A Clinicopathologic Analysis of 20 Cases

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Abstract

Background Lipoblastomas (LPBs) are benign adipocytic neoplasms believed to recapitulate the development of embryonal fat.

Methods We investigated the clinicopathologic and immunohistochemical features of 20 lipoblastomas arising in the head and neck in 18 patients.

Results Patients included 6 males and 12 females (1:2 ratio) with age at diagnosis ranging from 4 months to 28 years. Tumors occurred more commonly in the neck (12, 66.7%) and less commonly in the forehead, scalp, and tongue (2, 11.1%). Tumor size ranged from 1.4 to 6.0 cm (median 5.0 cm). Two patients, a 4-month-old female and 3-year-old male, had local recurrence of neck tumors at 4 months and 3 years after excision, respectively. Microscopically, tumors had a lobulated growth pattern and consisted of adipocytes at varying stages of differentiation. In addition to the classical histologic features, lipoma-like and myxoid variants constituted 45% of cases. Metaplastic elements, including brown fat and cartilage, were identified in two cases.

Conclusions LPBs arising in the head and neck region are not uncommon and occurred at a rate of 9% in our cohort. They should be kept in the differential diagnosis when a fatty tumor is encountered in an older child or occurring at an unusual location.

Keywords Lipoblast · PLAG1 · Lipoblastoma · Neck · Lipoma

Introduction

Lipoblastomas (LPBs) are benign adipocytic neoplasms believed to recapitulate the development of embryonal fat [1–3]. They typically arise as circumscribed, slowly growing masses on the extremities and or trunk, but occasionally they manifest in the head and neck region [1, 4]. These tumors are more commonly noted in males and most often, but not exclusively, occur during the first decade [1, 4, 5]. They present as localized or diffuse tumors with a tendency for local recurrence [1].

Histologically, the tumors are lobulated with a varying proportion of mature and immature fat cells separated by fibrous septa. Immunostains show frequent positivity for S100 protein, desmin, CD34, and PLAG1. LPBs are characterized by abnormalities of chromosome 8q11-13, resulting in rearrangement of the *PLAG1* gene with a plethora of partners [2, 6]. Rarely, genetic aberration of chromosome 12q14.3, resulting in rearrangement of the *HMGA2*, gene, is identified [6, 7].

We report a series of 18 patients with LPB occurring in the head and neck region to explore the clinical and pathologic feature of these tumors in this anatomic location.

Materials and Methods

This study was approved by the Institutional Review Board at Boston Children's Hospital. Twenty in-house LPB cases arising in the head and neck region between January 1987 and January 2020 were retrieved from the Boston Children's

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Hospital slide archives, Boston, MA. Consult cases were excluded. Hematoxylin and eosin-stained slides of all cases along with available immunohistochemistry were re-reviewed by the senior author.

Patients' age and sex, anatomic location of tumor, and size of tumor (maximal dimension) were recorded. When available, clinical information and follow-up were obtained from the electronic medical record. Immunohistochemical stains for PLAG1 (vendor catalog Abnova, H00005324-M02, antibody clone 3B7), desmin (vendor catalog Leica Biosystems, PA0032, antibody clone DE-R-11), and S100 (vendor catalog Agilent Dako, IR504, polyclonal antibody) were performed on 7, 9, and 3 cases, respectively. Anchored multiplex RNA sequencing assay was performed on one case. Briefly, RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue, followed by cDNA synthesis and library preparation using reagents provided by ArcherDX (Boulder, CO, USA). Gene targets varied by assay: a custom panel from Boston Children's Hospital Anchored multiplex polymerase chain reaction amplicons were sequenced on Illumina sequencers (HiSeq or MiSeq). Analysis was performed using the Archer Analysis software.

Table 1 Demographic and clinical features of lipoblastomas

Features	*n*/Total (%)
Age (median/range)	5.4 years/4 months to 28 years
Sex	
Male	6/18 (33.3)
Female	12/18 (66.7)
Locations	
Neck	12/18 (66.7)
Forehead	2/18 (11.1)
Tongue	2/18 (11.1)
Scalp	2/18 (11.1)
Tumor size (median/range)	5.0 cm/1.4 cm to 6.0 cm
Tumor characteristics	
Classic LB	11/20 (55)
Mature lipoma-like LB	6/20 (30)
Myxoid LB	3/20 (15)
Heterologous elements	
Cartilage	1/20 (5)
Brown Fat (hibernoma-like)	1/20 (5)
Local recurrence	2/18 (11.1)

Results

Clinical Features

Clinical and pathologic data are summarized in Table 1. The cohort consisted of 18 patients and included 12 (66.7%) females and 8 (33.3%) males. Patients' mean age at time of diagnosis was 5.5 years, with a wide age range (4 months to 28 years). Overall, the neck was preferentially involved, followed by forehead and scalp. Resected tumor specimens ranged in maximum dimension from 1.4 to 6.0 cm (median 5 cm). Tumors presented as asymptomatic soft tissue masses in most patients with the exception of a rapidly growing posterior neck mass in a 16-month-old male and persistent cervical lymphadenopathy in 3-year-old female. All patients underwent surgical excision of the primary mass. Re-excision was documented in two cases in which tumors had locally recurred. One case recurred in the right supraclavicular area of a 4-month-old female after 4 months and the second case recurred in the left posterior neck of a 3-year-old male 3 years post excision.

Pathologic Features and Immunohistochemistry

Histologically, typical areas of the LPB were distinctly nodular, consisting of lobules of fat in various stages of maturation surrounded by thick fibrous bands (Fig. 1). Six tumors had predominantly mature adipose tissue resembling lipoma, while eleven cases showed classic morphology composed of lobules of primitive mesenchymal cells, lipoblasts, and small capillaries (Figs. 1, 2). Prominent myxoid stroma was noted in three cases. One LPB arising in the tongue of a 3-year-old female exhibited striking nodular areas of mature and immature cartilage without atypia (Fig. 3). One tumor in the neck of 3-year-old with marked myxoid stroma exhibited prominent delicate vasculature with numerous uni- and multi-vacuolated lipoblasts mimicking myxoid liposarcoma (Fig. 4). Additionally, one case arising in the neck of a 3-year-old male had small foci of brown fat adjacent to the normal soft tissue components (Fig. 4).

As expected, all tumors were strongly immunopositive for PLAG1 (7/7), while desmin was positive in nine cases (9/11) and equivocal to negative in the remaining two cases. Three cases were positive for S100 protein (3/3).

Molecular Analysis

One case was confirmed to have *HAS2::PLAG1* fusion by RNA-based targeted fusion assay.

Discussion

LPBs are benign mesenchymal tumors arising from embryonal white fat which recapitulates the process of embryonic adipocytic differentiation [1–3]. LPBs occur at various sites but most frequently affect the trunk and extremities [4]. Previous studies of LPBs arising in the head and neck reported the incidence rate as 10–15% [8–10]. These series mostly

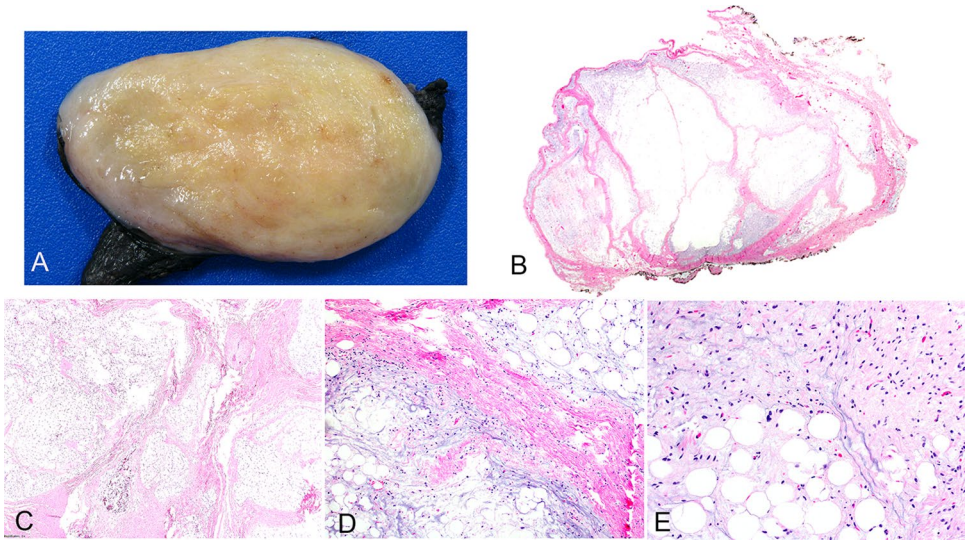

Fig. 1 Common histological features of lipoblastoma. **A** Grossly, LPB is a circumscribed mass with a yellow vaguely nodular cut surface. **B** Most tumors exhibited classic features of LPB with an encapsulated lobulated growth pattern and intervening thin fibrous bands. **C** Focal areas exhibited myxoid stroma. **D** and **E** Immature lobules consist of primitive mesenchymal cells admixed with mature adipocytes

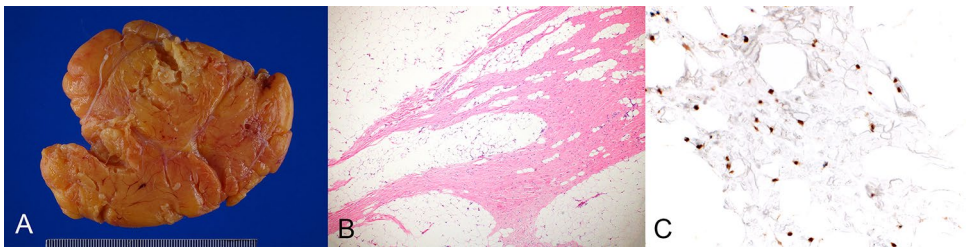

Fig. 2 Lipoma-like lipoblastoma. **A** Grossly, a lobular brown mass with focal myxoid cut surface (left). **B** A multilobulated architecture of mature adipocytes with dense intervening fibrous bands. **C** Immunohistochemical stain for PLAG1 reveals strong nuclear positivity correlating with the presence of gene fusion

highlight radiologic and clinical features, while reports of pathologic features are limited to case reports, small series, or as part of large series of LPB involving all sites. Herein, we are reporting the largest series of LPB involving the head and neck region and in doing so we are highlighting the distinct pathologic features of these tumors. In our cohort, we report a rate of 9% of total LPB resected in our institution (20 out of 243 total LPB during the study period). As in prior reports, most LPBs in our series occurred in the neck (66.7%). To date, cases of LPBs in other head and neck sites have been documented in the literature in the parotid gland [11, 12], cheek [13, 14], tongue [15, 16], and orbit [17, 18]. Our cohort included forehead and scalp. A recent systematic review reported that the incidence of LPBs was more common in males (55%) with a median age of 3.30 years (range 2 months to 20 years) [8]. In our cohort, LPBs were more frequent in females (66.7%) and in patients older than 3 years of age with a wider overall age range (range 2 months to 28 years).

The most common rearrangement of LPBs involves the 8q11-13 region affecting the *PLAG1* gene. Since its discovery, various fusion partners of *PLAG1* have been reported in LPB including *HAS2, COL1A2, RAD51B, COL3A1, RAB2A, BOC, CHCHD7, HNRNPC, SRSF3, PCMTD1, YWHAZ, CTDSP2, PPP2R2A, DDX6, KLF10, KANSL1L, PI15, and ZEB2* [2, 6, 19–26]. Recently, novel *HMGA2* fusions have been documented in LPB, some of which are associated with *EP400 and FGD6* as partners [6, 7]. This gene translocation event results in the upregulation of *PLAG1* or *HMGA2* by a promoter swapping mechanism [2]. Other chromosomal abnormalities include polysomy and ring chromosome involving chromosome 8 [2, 27–29]. The *HAS2::PLAG1* fusion gene was identified in the single case tested in our cohort.

As expected histologically, the majority of our cases demonstrated lobular architecture. These lobules were composed of fat cells in various stages of differentiation separated by fibrous septa, recapitulating developing fat. Among histologic subtypes, the myxoid variant and lipoma-like variant were equally noted in addition to the classical variant. Although metaplastic elements such as cartilage and bone are documented in benign and malignant adipocytic tumors [30, 31], their presence in LPB is not common [32]. Here, we found metaplastic mature

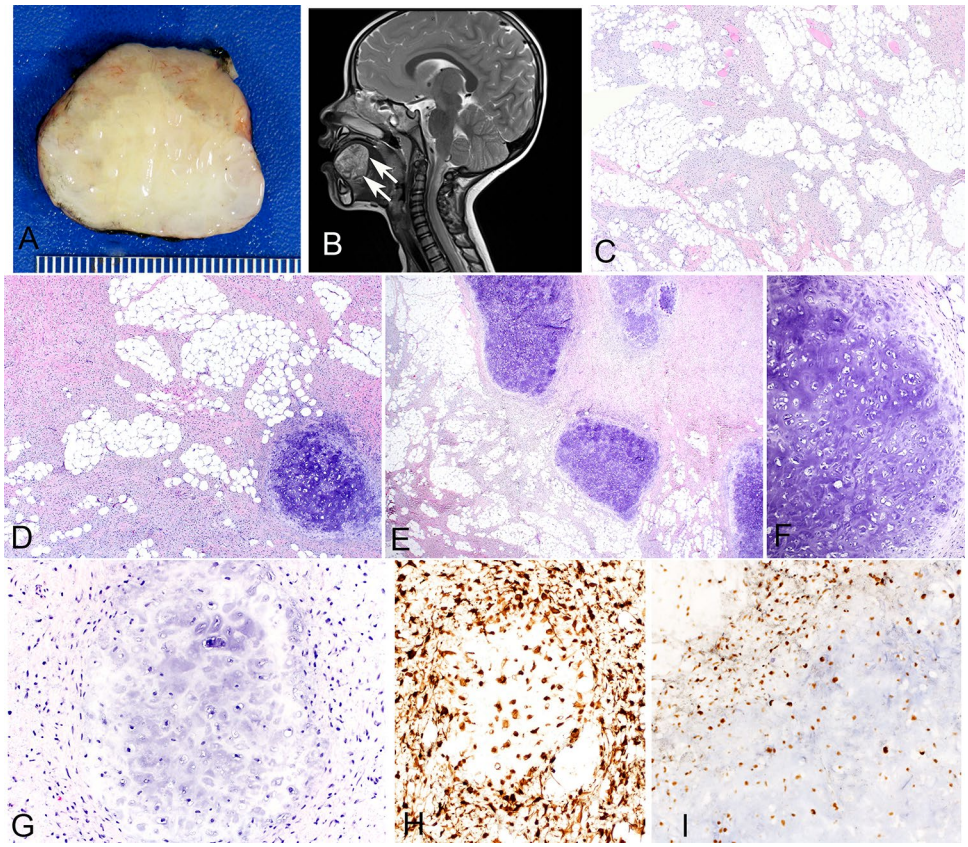

Fig. 3 A 3-year-old female with tongue lipoblastoma. **A** Grossly, a round mass with a bright yellow surface macroscopically. **B** Preoperative sagittal MRI image of the head and neck reveals a well-delineated lingual mass (white arrows). **C** LBP showing lobules of fat in various stages of maturation, surrounded by thick fibrous bands. **D** Lobules consist of primitive mesenchymal cells admixed with mature adipocytes and a nodule of immature cartilage. **E–G** Multiple foci of cartilage in between the adipocytic lobules consist of primitive mesenchymal cells admixed with mature adipocytes. **H** Immunohistochemical stain for desmin shows strong positivity within lesional cells. **I** Immunohistochemical stain for PLAG1 reveals strong nuclear positivity. Note that positive staining includes both primitive cells and metaplastic cartilage

and immature cartilage in a tongue location. Immunohistochemical studies showed that tumors, including the metaplastic cartilage and primitive stroma cells, were positive for desmin and PLAG1, confirming the diagnosis of LPB (Fig. 3). In our cohort, only seven cases had PLAG1 immunostain performed. None of these cases had classic LPB histologic features, 5 were maturing lipoma-like, one with metaplastic cartilage, and one with marked myxoid matrix. The latter case occurred in the neck of a 3-year-old female and exhibited prominent vascular pattern reminiscent of "chicken wire" vasculature seen in myxoid liposarcoma, although this is a less likely diagnostic consideration at age 3. Additionally, this case had the fusion panel performed documenting the presence of a *HAS2::PLAG1* gene fusion. Overall, we believe that a combination of PLAG1 and desmin immunohistochemical staining may be of particular utility when LPB is encountered in an unusual clinical setting (i.e., older children/young adult) or exhibiting unusual morphologic features such as maturation or metaplastic elements. Positivity for PLAG1 within the chondroid component of our case supports the divergent differentiation of tumor cells theory leading to over stimulation of stromal resident multipotent undifferentiated mesenchymal cells [33]. We noted one case with hibernoma-like foci in line with a previously described pattern in a cytogenetically confirmed case [21].

Similar to any other site, the differential diagnosis of LPB in the head and neck region is based on histologic subtypes. LPB with a predominant mature lipomatous morphology mimics lipoma but the latter lacks the lobular growth and PLAG1 rearrangement [34]. A patient with PIK3CA-related overgrowth spectrum (PROS) disorder that exhibits features similar to those lipoma-like LPB with focal fibrous septa has been described [35, 36]. That case occurred in the posterior neck of 3-month-old male and presented as a solitary mass involving the subcutaneous tissue [36]. Thus, molecular testing to look for potential PIK3CA mutation is important to confirm the diagnosis in patients with localized fatty overgrowth instead of an isolated lipomatous tumor [36]. LPB with predominantly myxoid morphology should be distinguished from myxoid liposarcoma, which is extremely rare in children and exhibits distinctive delicate vasculature in a "chicken wire" pattern and lacking prominent lobulation [37]. Recently, the detection of gene t(12;16)(q13;p11) involving the *DDIT3* and *FUS* genes can aid in confirming the diagnosis of myxoid liposarcoma [38]. Predominantly myxoid LPB with metaplastic elements represents a potential diagnostic pitfall by mimicking pleomorphic adenoma with chondroid stroma [39]. The mesenchymal component produced by myoepithelial cells may be myxoid/mucoid, osseous/cartilaginous, or hyalinized. The lipomatous stromal component varies from tumor to tumor

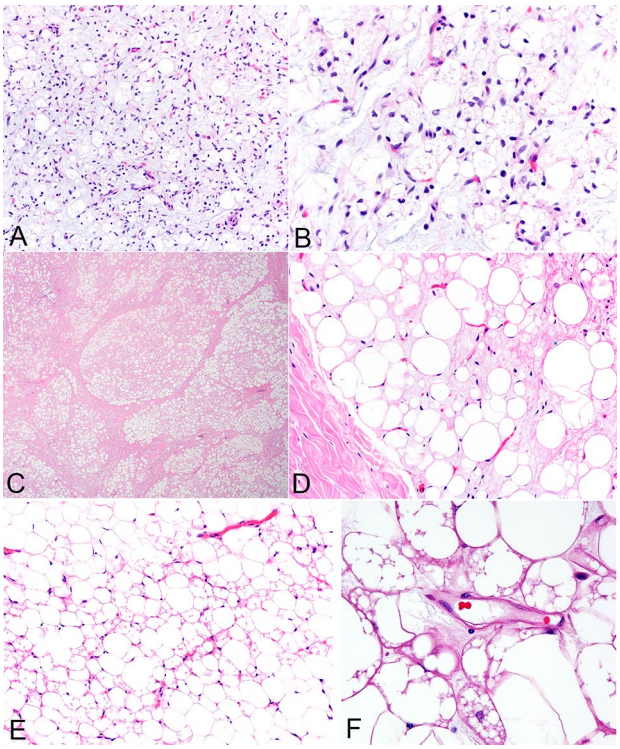

Fig. 4 **A** and **B** *HAS2::PLAG1* fused lipoblastoma in the neck of a 3-year-old female showing marked myxoid stroma with a delicate vascular pattern and numerous lipoblasts. **C**–**F** Lipoblastoma in the neck of a 3-year-old male showing a classic lobulated pattern with myxoid stroma and variable adipocytic maturation (**C**, **D**) in addition to foci of "hibernoma-like" brown adipose tissue with multi-vacuolated adipocytes (**E**, **F**)

and if it constitutes > 90% of tumor tissue, it is considered a lipomatous pleomorphic adenoma [40, 41]. Molecular alterations involving the *PLAG1* gene are found in LPB and pleomorphic adenoma. Unlike LPB, pleomorphic adenoma consists of a proliferation of ductal structures and myoepithelial cells [42, 43]. For LPB with a predominantly primitive and fibroblastic component, the differential diagnosis includes fibrous hamartoma of infancy and lipofibromatosis. Fibrous hamartoma of infancy is less circumscribed and displays triphasic morphology with variable percentages of fat, fibroblastic fascicles, and primitive mesenchyme [44]. While lipofibromatosis often presents as a growing mass of the distal extremities and consists of an infiltrative admixture of mature fat, lipoblast-like cells, and fascicles of bland uniform fibroblastic/myofibroblastic cells [45].

In summary, we have reported the clinicopathological and immunohistochemical features of the largest series of head and neck LPBs to date. Our results confirm and extend prior observations about this pediatric adipocytic tumor. LPBs arising in the head and neck region are not uncommon and occurred at a rate of 9% in our cohort. They showed typical morphologic features of lobules of fat in various stages of maturation surrounded by thick fibrous bands. LPB should be kept in the differential diagnosis when a fatty tumor is encountered in an older child or occurring at an unusual location. In general, the diagnosis can be rendered based on histologic features alone. However, on rare occasions, particularly in tumors occurring outside the classic clinical setting, ancillary studies may be of value.

Author Contributions ZA conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; AA-I reviewed the pathology slides, revised the manuscript, created the figures, and critically reviewed the manuscript for important intellectual content; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data Availability N/A.

Code Availability Data availability statements provide a statement about where data supporting the results reported in a published article can be found including, where applicable, hyperlinks to publicly archived datasets analyzed or generated during the study: N/A.Consent for Publication N/A.

Declarations

Conflict of interest No conflict of interest to disclose.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent N/A.

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