Lipoblastomatosis of the retropharyngeal space: pathogenesis, presentation, and management, with a focus on head-neck lipoblastoma(toses)

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Abstract. Lipoblastomatosis of the retropharyngeal space: pathogenesis, presentation, and management, with a focus on head-neck lipoblastoma(toses). Objective: Lipoblastoma(toses) are benign neoplasms of embryonic white fat in a state of arrested maturation, and are seldom encountered in the head-neck region. We discuss the clinical details of lipoblastomatosis in the retropharyngeal space of a 9-year-old boy, with an emphasis on the head-neck area, the histopathological maturity of the tumor, and the practical roles of imaging, cytogenetics, and immunostaining in the diagnosis. Methods: Clinical record analysis; literature review. Results: A malnourished child presented with worsening respiratory distress and feeding difficulties. Imaging suggested a large, heterogeneous fibrofatty lesion in the retropharyngeal space. Surgery revealed an otherwise encapsulated mass that densely adhered to the pre-vertebral soft tissue. The findings were consistent with a diagnosis of maturing lipoblastomatosis on histopathology, which was supported by additional immunohistochemistry panel analysis. Conclusion: This is the first report of lipoblastomatosis with the retropharyngeal space as the epicenter of involvement/origin. Although rare and seldom diagnosed before surgery, lipoblastoma(tosis) may be more common in the head-neck area than thought previously and should be an important differential diagnosis for pediatric fibrolipomatous neoplasms in this anatomic subsite.

Introduction

Lipoblastoma(toses) are benign neoplasms of embryonic white fat in arrested maturation that are seen almost exclusively in neonates and young children (<3 years old).¹⁵ Several record reviews of pathology databases indicate that they are currently recognized as important lipomatous tumors of the head-neck area. Their pathobiological characteristics, as determined by histology and imaging studies, indicate that they are heterogeneous in terms of maturation stage, ranging from predominantly lipoblastic to lesions that are identical to lipomas, making them difficult to diagnose. Here we present and discuss the clinical record of a child with lipoblastomatosis in his retropharyngeal space and highlight the cardinal features of this unusual tumor in terms of presentation, diagnosis, and management.

Case report

A 9-year-old malnourished boy presented with intermittent respiratory distress and feeding difficulties that had persisted for the past 5 years and that had worsened in the last 8 months. On examination, his posterior pharyngeal wall bulged anteriorly, partly compromising the upper aerodigestive tract. Although not common in this age group, we initially considered chronic retropharyngeal abscess. Accordingly, we performed a contrast-enhanced computed tomography (CECT) scan that revealed a large non-enhancing heterogeneous mass in the retropharyngeal space corresponding to all three pharyngeal segments (Figure 1A-D). However, the signal intensities suggested a fibrofatty lesion, and there was no ring enhancement, ruling out retropharyngeal abscess. The routine
my (Rose’s) position was preferred, as this would give us good access to the mass for the purpose of incisional biopsy. We intended to use the least invasive approach as the lesion appeared in the midline by radiology. Since the airway seemed patent enough and the child never had stridor, he

hematology reports were unremarkable, as were other physical examination findings, except that the child weighed only 24 kg.

Unable to reach a provisional clinical diagnosis, we planned an incisional biopsy under general anesthesia. An intra-oral approach in the tonsillectomy...
was not tracheostomized and could be intubated safely. However, at surgery, an approachable surgical plane could be delineated between the pharyngeal wall and the mass proper. The lesion was well-encapsulated, free on all sides; thus, we decided to explore further with hopes that the mass could be removed in toto. However, during the course of the dissection, we observed that the lesion had dense adhesions posteriorly with the pre-vertebral tissue, and its inferior extent was not visible with the endotracheal tube in-situ. The child was therefore extubated, and the airway was secured by temporary tracheostomy. The mass was excised piece-meal owing to the posterior adhesions. Subsequent histopathological analysis revealed mature lobulated adipocytes that were focally associated with loose myxoid matrix. They were separated by unusually thick and cellular fibrous septae with short spindle cells and branching vessels and lacked any mitoses or nuclear atypia (Figure 2A-E). The findings were consistent with a diagnosis of maturing lipoblastomatosis. The specimen showed positive staining for cluster of differentiation (CD)-34 and negative staining for calponin, Ki-67, beta-catenin, and smooth muscle antigen (SMA) (Figure 3A-E).

The child recuperated well without any major post-operative complications. He was discharged a week later and was successfully decannulated after four weeks. Subsequent magnetic resonance imaging (MRI) performed two months following surgery revealed no residual mass (Figure 4). His weight gain was satisfactory, and there was no evidence of recurrence at the 1-year follow-up.
In the few single case records of head-neck lipoblastoma(tosis), there is a predilection for the paraspinal and supraclavicular regions. However, a thorough search of the PubMed/MEDLINE® database failed to retrieve any reports of lipoblastoma(tosis) that primarily involved the retropharyngeal space. In the only other case in which this region was involved (Capasso et al.12), the lesion actually originated in the supraclavicular fossa and later encroached on the retropharyngeal space, infiltrated the trachea, and reached the contralateral side. The adhesion to the pre-vertebral tissue noted in our case was also seen in some previous reports in which lesions in the paraspinal region tended to adhere and infiltrate through the spinal foramina.5,13 The term “lipoblastomatosis” is used exclusively for such infiltrating, deep-seated, multifocal forms; in contrast, “lipoblastomas” are well-circumscribed, encapsulated, superficial, and potentially removable in toto.4,14 However, they might exhibit a dual nature,15 as in the present case where the tumor was partly circumscribed with a demonstrable tissue plane. Therefore these terms are apparently not entirely distinct and are better used to describe the differential host/tumor tissue interaction that co-exists in the same specimen.

Histologically, lipoblastomas represent lobulated adipocytes in various stages of maturity that are interspersed by fibrous strands.4,14 As in our patient, the pattern can be so variable that it is practically an intermediate form between the most immature adipocytic tumor and a lipoma. As they mature, the multi-vacuolated adipocytes become mono-vacuolated (the “signet-ring” stage) and increase at the expense of lipoblasts; concurrently, the myxoid element and spindle cells decrease. Provided this transition does not get interrupted by symptom production and subsequent surgical removal, an immature lipoblastoma can theoretically transform into a tumor akin to a lipoma. This transition has

Discussion

Lipoblastomatoses predominantly involve the extremities and torso, including the retroperitoneum and mediastinum,1 and are considered to be uncommon in the head-neck region. However, a review of archived institutional pathology records revealed that involvement of the head-neck region ranges from 8%-31% (average 17%) (Table I).2-11 It thus seems that the disease might be underdiagnosed or under-reported in the head-neck region. We consider the head-neck region to be an important area of interest and look upon lipoblastoma(tosis) in this anatomic subsite to be a relatively unknown, seldom-discussed disease entity with which otolaryngologists dealing with pediatric airway cases should be aware and familiar.

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Lipoblastoma(tosis) is seldom suspected at initial presentation, which can be dramatic with compression symptoms. This is particularly true for head-neck lipoblastoma(toses) in the vicinity of the upper airway, which could cause children to present with exacerbations. As for superficial sites, the scope of cellular diagnosis is limited in deep-seated lesions because of non-representative aspirate. Open biopsy and frozen section are preferred, but may not always be helpful. Imaging should give an idea about the consistency and extent of the lesion. Ultrasonography shows heterogeneous hyperechogenicity for fat, while CT images are hypodense (less dense than subcutaneous fat in immature lipoblastomas) with weak signals for fibrous strands. MRI appears to be more informative: there is hypointensity in early T1-weighted images and hyperintensity in T2-weighted images (due to excess myxoid component). With maturity, the T1-weighted images become hyperintense and, unlike subcutaneous fat, this persists even with fat-suppression.

MRI is thus an important follow-up imaging tool, and the specific tumor characteristics should be kept in mind when examining follow-up images for any residual/recurrent lesions. The signal heterogeneity appears to depend upon the proportion of lipoblasts, mature adipocytes, myxoid, and fibrous components, although pathognomonic diagnostic features are lacking. Interestingly, the

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Table I

Major institutional archival reviews of studies on lipoblastoma(tosis) published in the last two decades reveal that there is involvement of the head-neck region in 8%-31% of cases (average about 17%)

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Citation</th>
<th>Year of publication</th>
<th>Sample size</th>
<th>Involvement of the head-neck region (%)</th>
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<tr>
<td>1.</td>
<td>Fallon SC et al.</td>
<td>2013</td>
<td>37</td>
<td>16</td>
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<td>2.</td>
<td>Kok YY, Telisinghe PU</td>
<td>2010</td>
<td>10</td>
<td>30</td>
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<td>3.</td>
<td>Coffin CM et al.</td>
<td>2009</td>
<td>59</td>
<td>8</td>
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<tr>
<td>4.</td>
<td>Speer AL et al.</td>
<td>2008</td>
<td>32</td>
<td>9</td>
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<td>5.</td>
<td>McVay MR et al.</td>
<td>2006</td>
<td>16</td>
<td>16</td>
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<td>6.</td>
<td>Jung SM et al.</td>
<td>2005</td>
<td>16</td>
<td>31</td>
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<td>7.</td>
<td>Hicks J et al.</td>
<td>2001</td>
<td>26</td>
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<td>8.</td>
<td>Hicks J et al.</td>
<td>2001</td>
<td>170</td>
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<tr>
<td>9.</td>
<td>Chun YS et al.</td>
<td>2001</td>
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* = Literature review.

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...actually been demonstrated, which is why tumors with adhesions (lipoblastomatosis) and neurovascular encasement are preferably resected incompletely to prevent mutilation and morbidity. This practice leads to natural disease progression, which is slow and unpredictable, necessitating prolonged follow-up for possible recurrence. Because it is difficult to detect this transition and because there is a meaningful chance of recurrence (up to 15%-27%), complete surgical excision is favored wherever feasible. In this particular case, we had to remove the retropharyngeal space tumor piece-meal due to adhesion; although subsequent MRI revealed no residual lesion, we are wary of future recurrence from a possible microscopic tumor-tissue remnant and have continued to observe the child closely. The recent concept of understanding the "epicenters of tumor burden" for lipoblastomatosis promises to help surgeons identify the primary focus as the starting point of surgery and to plan the extent of resection accordingly without functional compromise. Resection could range from piece-meal excision/debulking to, ideally, complete removal if possible. Notably, the epicenter theory differentiates our patient with the retropharyngeal space as the primary site of origin from the one described by Capasso et al.; in the latter case, this region was only involved secondarily. This makes the current case unique and unprecedented.

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patient’s age seems to be unrelated to the degree of maturation. Gardikis et al.19 in their account of a 13-month-old child, found no myxoid stroma, which is considered a marker of immaturity. The histologic transition might even be retrograde, as a previously mature lipoblastoma may show primitive features upon recurrence. Further, it is not true that lipoblastomatoses are always deep-seated or that a lipoblastoma never recurs. Interestingly, it seems that the infiltrative nature of the lesion has little bearing on recurrence. Therefore, given the complexity of the pathobiogenesis of lipoblastoma(tosis) and its variable clinicoro-adological presentation, pre-operative diagnosis is truly the “exception rather than the rule.”

Currently, cytogenetic study is the most definitive way to diagnose lipoblastoma(tosis). Chromosome 8 abnormalities are highly characteristic, and the role of leptin and its receptors is being investigated. Among the genetic changes identified to date, 60%-70% are PLAG1 rearrangements in chromosome 8q12 and translocations at 8q11-13, with chromosome 8 polysomy seen in 18% of cases. This helps exclude myxoid liposarcoma (chromosome 16 abnormalities and TLS-FUS/CHOP translocation on chromosome 12) and lipoma (abnormalities in chromosomes 12 and 13), which are close differential diagnoses. Other entities that are often considered include lymphangioma, hibernoma, teratoma, dermoid cyst, and hemangioma. However, cytogenetic analysis is often not feasible due to prohibitive cost or to the unavailability of appropriate laboratory facilities or supplies such as specialized (Roswell Park Memorial Institute) transport media or specific probes. Moreover, the tissue must be fresh (<24 hours) for the analysis; so there needs to be a high index of suspicion from the treating surgeons before such tissue can be procured.

The chromosome 8 abnormalities include fusion-transcript PLAG1/HAS2, which along with PLAG1/COL1A2 (chromosome 7) are considered key regulators of the “maturation arrest” of embryonic mesenchymal adipocytes. Both hyaluronic acid synthase and collagen prepare the matrix for lipoblastoma(tosis), and aberrant production of these might explain the unusually thick cellular fibrous stroma in our patient. Although this is difficult to prove, it might also be due to the older age of the child and the prolonged course of the disease. These atypical features prompted us to consider Gardner’s fibroma and lipofibromatosis as additional differential diagnoses. However, the boy had no stigmata which were characteristic of Gardner’s fibroma, in which the matrix is predominantly fibrous with only “trapped” islands of fat. Lipofibromatosis is a recently-described, extremely rare entity, but the adipocytes in our patient were characteristically lobulated without the complex interplay with fibrous strands seen in typical infantile lipofibromatosis. In addition, the stroma was comparatively hypocellular with adipocytes and myxoid components even in the most fibrous areas. Immunohistochemistry is not necessarily following histological diagnosis, but we performed an immunohistochemical panel to further characterize the lesion and to exclude the differential diagnoses. Negative staining for SMA and beta-catenin argued against lipofibromatosis and Gardner’s fibroma, respectively. Our specimen was positive for CD34 and negative for Ki-67 (negligible proliferation potential). This is the only single-case documentation of lipoblastoma(tosis) requiring immunohistochemical analysis. The results were in accordance with those in the archived record-review of 43 subjects by Coffin et al., the only study with detailed immunohistochemical analysis of lipoblastoma(tosis), which found universally positive CD34 and S-100 staining and negative Ki-67 staining.

Conclusion

The present report is the first to describe midline lipoblastomatosis with an epicenter of tumor-tissue origin in the retropharyngeal space. The child presented late (age 9 years), lending credence to the current thinking that older children and adolescents might present with this lesion, with the head-neck region increasingly being an area of interest. Pre-operative diagnosis is difficult and requires pediatricians and otolaryngologists who are treating children with compressive symptoms to consider the possibility that a heterogeneous fibrofatty lesion that is contiguous with the cervical spine may be lipoblastoma(tosis). This lesion has a good prognosis with no metastasizing potential, but it might recur if it is incompletely removed, necessitating stringent follow-up. This report highlights the spectrum of histological features, the ambiguity of imaging and cytology findings, and the possible role of cytogenetics and immuno-
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histochemistry in diagnosing lipoblastoma(tosis) by describing a unique case in the head-neck region.

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References


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