LIPOMATOUS HEMANGIOPERICYTOMA OF THE HEAD AND NECK: IMMUNOHISTOCHEMICAL AND DNA PLOIDY ANALYSES

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Abstract: Background. Lipomatous hemangiopericytoma (LHPC) is a newly described rare soft tissue tumor with unpredictable biologic behavior and is difficult to diagnose by conventional histologic parameters. The molecular analyses of this entity to date are sparse. Only a few cases of LHPC have been reported. Although one case of LHPC in the sinonasal region was briefly reported, this is the first case in the head and neck region with detailed clinicopathologic features and molecular analysis of this entity.

Methods. We report a case of LHPC in a 55-year-old woman with a slowly growing lesion in the occipital area that was diagnosed by CT and MRI and removed surgically. Immunohistochemical and DNA ploidy analyses were performed.

Results. A panel of 16 markers was included for immunohistochemical analysis. Diffuse immunopositivity of CD57 in our case provides supportive evidence that LHPC is linked with HPC because this marker is also present in approximately 50% of conventional HPCs. CD57 should be used in the immunohistochemical panel in any lesion suspected to be LHPC. Furthermore, CD57 along with CD34 and XIIIa is thought to stain for primitive mesenchymal stem cells, suggesting a bimodal/multimodal differentiation of LHPC. By flow cytometry, we found that tumor cells were 100% diploid with the S-phase fraction (SPF) being 3.21%. A significant positive correlation was detected between nuclear proliferating index and SPF (p < .001, by Spearman analysis). These findings provide molecular evidence indicating a benign nature of LHPC.

Conclusions. Contrary to the old belief that HPC has an aggressive nature, this variant of tumor looks less aggressive. The patient was followed for 1 year without any evidence of recurrence, supporting our pathologic hypothesis.

Keywords: lipomatous hemangiopericytoma; CD57; DNA ploidy; proliferation index

Hemangiopericytoma (HPC) is uncommon mesenchymal tumor, accounting for 1% of all blood vessel–related neoplasms and approximately 3% of all soft tissue sarcomas.1–3

More than 50 years ago, Stout and Murray coined the term “HPC” for a unique vascular tumor characterized by branching capillaries surrounded by what they believed to be neoplastic pericytes. It is thought to demonstrate differentiation toward the pericytes of Zimmermann,
which lie external to capillary endothelial cells and function in changing the size of the vascular lumina\textsuperscript{4} regulating the capillary blood flow. Additionally, data suggest that they may also function as progenitor cells for developing adipocytes.\textsuperscript{5}

Despite the potential relationship between pericytes and adipocytes, tumors demonstrating both fatty and HPC features have been rarely documented.\textsuperscript{6}

HPC occurs predominately in the lower extremities and retroperitoneum. However, approximately one third of these neoplasms arise in the head and neck region.\textsuperscript{7} A seeming paradox exists regarding head and neck HPC as compared with HPC in other sites, such as the pelvis and lower extremities. The head and neck lesions are rarely reported to be malignant; however, those of the extremities and pelvis have significant rates of metastasis.

Lipomatous HPC (LHPC), a newly described variant, is an uncommon soft tissue tumor. Only one case of LHPC of the head and neck region has been reported. The molecular analyses of this entity are sparse. Herein we report a case of a large LHPC occurring in the occipital region and upper neck, as we describe its clinicopathologic features and the findings of immunohistochemical and DNA ploidy, and S-phase fraction (SPF) analyses.

**CASE REPORT**

A 55-year-old white woman in her usual state of health was admitted with a neck mass. The mass had been present for 10 years and had grown after a recent accident. Her medical history was significant for endometriosis and tonsillectomy. Physical examination revealed a large, palpable mass in the occipital area and upper neck; it had indistinct boundaries, was mildly tender, and showed no

**FIGURE 1.** (A) Contrast-enhanced CT scan demonstrates a mass with pushing border (straight arrows) in the middle line of occipital area. Portions of the mass are hypoattenuated, consistent with the presence of fat. (B) MR image confirms a well-circumscribed and vessel-rich mass without infiltration of the surrounding tissue. (C) LHPC shows small oval and rounded cells arranged around compressed and ectatic small vessels as well as large hyalinized vessels. Mature fat was present throughout the lesion (original magnification, \( \times 200 \)). (D) The tumor is surrounded by a thin fibrous pseudocapsule (left). Myxoid areas are evident (original magnification, \( \times 100 \)).

**FIGURE 2.** Photomicrographs show results of immunohistochemistry. Note in various sections that the tumor is composed of an admixture of adipocytes and spindle cells with prominent staghorn branching of the vascular bed. (A–F, original magnification, \( \times 100 \); G and H, original magnification, \( \times 200 \).) Antibodies were as follows: CD34 (A), S-100 (B), CD99 (C), XIIa (D), Bcl-2 (E), CD57 (F), and Mib-2 (G; note only few positive nuclear stained cells present [in the central field]), and p53 (H). More than 50% of tumor cells stained positive.
visible pulsation. No evidence of peripheral adenopathy or cutaneous abnormality was present.

CT revealed a solitary heterogeneously enhancing mass (10 × 6 × 5 cm) with hypoattenuating areas in the posterior soft tissues of the neck compressing other soft tissue without spinal involvement (Figure 1A). MRI confirmed a well-circumscribed, lobulated, enhancing lesion on two-dimensional images, with increased vascularity without infiltration of the surrounding tissue (Figure 1B). The results of laboratory studies were within normal limits. An incisional biopsy was performed, resulting in the early diagnosis of spindle cell lipoma (SCL). Subsequently, a wide local excision was performed, resulting in the final diagnosis of LHPC. The patient had an uneventful postoperative course. Postoperatively, she showed no evidence of disease at 12 months’ follow-up.

Pathologic Findings. The tumor, grossly 9 × 6 × 4.5 cm in size, was well demarcated with a lobular configuration. The cut surface of the tumor had a whitish-tan appearance with a rubbery consistency. Yellowish, grossly fatty regions were scattered through the mass. Microscopically, the tumor exhibited a lobular growth pattern and was composed of cellular areas with the classic appearance of HPC admixed with clusters and lobules of mature adipocytes (Figure 1C). A thin rim of fibrous tissue was noted at the periphery (Figure 1D). The HPC regions showed characteristic branched staghorn vessels, perivascular and interstitial hyalinization, and round-to-oval mesenchymal cells with relatively little atypia. The nuclei were uniform and spindled, and the cells had scant cytoplasm. Mitotic activity was infrequent (<2 mitotic figures/10 high-power fields). In some areas, the spindle cells were somewhat separated by myxoid ground substance (Figure 1D). No lipoblasts were identified. The tumor was positive for CD34 (Figure 2A).

Immunohistochemical Analysis. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue using the avidin-biotin peroxidase complex method, as previously described. The panel of antibodies analyzed included vimentin, α-smooth muscle actin (SMA), muscle-specific actin (MSA), desmin, S-100 protein,
XIIIa, Bcl-2, Mib-1 (Ki-67), p53, CD31, CD34, CD57 (Leu-7), CD99 (MIC-2), CD117 (c-kit), glial fibrillary acidic protein (GFAP), neurofilament, epithelial membrane antigen (EMA), and cocktail cytokeratin (AE1/AE3) (Table 1).

The tumor cells were diffusely positive for vimentin, CD34, CD57, CD99, Bcl-2, XIIIa, and S-100 (Figure 2). Approximately 50% of the tumor cells were positive for p53, whereas Mib-1 stained only 3% of tumor cells (1000 cells counted). Occasionally, focal reactivity was also observed for SMA. MSA stained only the blood vessels. No immunoreactive deposits were observed in the sections stained with desmin, CD117, neurofilament, EMA, and AE1/AE3 (Table 1).

Flow Cytometry. Flow cytometry was performed by the standard method. Although accurate cell cycle analysis could not be performed owing to cell debris (28%), all cells analyzed showed diploid (modeled events: 14,831; all cycle events: 9277; cycle events per channel: 168): diploid G1, 96.47%; diploid G2, 0.32%; and diploid S-phase fraction, 3.21% (% confidence variable [CV]: 3.35) (Figure 3). A significant positive correlation was found between nuclear proliferating score and SPF ($p < .001$, by Spearman analysis).

DISCUSSION

In 1995, Nielson et al$^9$ reported three cases of distinctive tumor composed of mature adipocytes and hemangiopericytomatosus areas for which they proposed the term LHPC.

Previously reported observations have shown LHPC to occur in middle-aged adults, with no predilection by sex. Most lesions present as longstanding, deep-seated, indolent tumors discovered accidentally, with possible compression symptoms due to mass effect. To date, a total of 33 LHPC cases have been reported in the English literature.$^{10–12}$ The patients were 20 men and 13 women whose ages at diagnosis ranged from 27 to 75 years (median, 48 years); all presented with a mass of various durations. Tumor size ranged from 1.7 to 21 cm (median, 5.5 cm). Most LHPCs occurred in the retroperitoneum and the lower extremities, and the rest were located elsewhere in the deep soft tissue. Although the follow-up is too short to draw definite conclusion, LHPC appears to be a slowly growing benign mesenchymal neoplasm with little propensity for local recurrence, especially in the head and neck region.

It is difficult to correctly diagnose this entity on the basis of clinical and radiologic information alone. The pathologic differential diagnosis of this case included SCL, liposarcoma, myxoid dermatofibrosarcoma protubers (DFSP), and solitary fibrous tumor (SFT). Although SCL and LHPC are composed of bland-appearing spindle cells, SCL has wire-like collagen fibers and lacks the ramifying vasculature of varying caliber found in LHPC. Liposarcomas, especially the myxoid variant, can have a prominent vasculature. The vessels in these tumors are delicate, small-caliber capillaries arranged in a plexiform branching pattern, different from the staghorn configuration of HPC. Although areas of low-grade dedifferentiation are encountered in 10% of cases of dedifferentiated liposarcoma, they usually assume the appearance of low-grade fibrosarcoma.$^{13}$ The few cases of spindle cell liposarcoma that have been reported have had distinctly and uniformly atypical spindle cells that can be recognized as histologically malignant. Common to all types of liposarcomas and required for their diagnosis is the presence of lipoblasts,$^{14}$ which were not identified in our case or any of the reported cases of LHPC. Lack of classic storiform growth pattern and presence of fibrous rim around the mass, along with it being deep beneath the subcutaneous fascia, argue against DFSP.

Whereas some areas resemble classic HPC, SFT usually shows areas of haphazard growth, distinct fascicles composed of spindled cells, broader areas of hyalinized stroma, and growth as single cells and short chains of cells.$^{13,14}$ A recent study suggested that LHPC is closely related to SFT, based on their similar clinical, pathologic, immunohistochemical, and ultrastructural features. In fact, as experience accumulates, there is growing evidence that LHPC and SFT significantly overlap, and it is likely that most LHPCs are merely fat cell–containing variants of SFT. The following observations support this concept: (1) both LHPC and SFT are encapsulated, deep-seated lesions; (2) both occur during middle age, without a sex predilection; (3) both behave as slow-growing nonrecurring lesions; (4) both might contain a small amount of fat; (5) the majority of LHPCs show SFT morphology; (6) most LHPCs and SFTs show reactivity to CD34 and CD99; and (7) both exhibit similar ultrastructural features in keeping with fibroblast, myofibroblast, and/or pericyte differentiation.$^{11}$

Another consideration in the differential diagnosis is HPC with fat trapping. Arguments
Lipomatous Hemangiopericytoma against this possibility include the following: (1) LHPC has been reported in anatomic sites where fat does not exist; (2) most cases, including ours, were encapsulated or with pseudocapsule formation, suggesting that fat was an integral component of the neoplasm; and (3) the distribution of fat was relatively even throughout the lesion (ie, just as prominent in the central area of the neoplasm as in the tumor periphery), which would make the possibility of entrapment of fat unlikely.

Whether conventional HPC in the sinonasal region (nasal passages and paranasal sinuses) is the same entity as HPC in other regions of the body remains debated. Microscopically, HPCs from the sinonasal region differ slightly from those occurring elsewhere in the body. The former tend to have cells with a greater amount of cytoplasm, vaguely reminiscent of glomus cells, have a more prominent spindle cell pattern, and are less vascular. Because of these variations, the term “hemangiopericytoma-like tumors” was also used to describe these lesions; this term was first coined because of the seemingly innocuous behavior of the first-collected head and neck cases, as compared with the more aggressive behavior of soft tissue/axial-skeletal HPC. In the latter group, distant metastases, especially to the lung and soft tissues, have been reported to occur in as many as 64.5% of patients, along with a significant rate of local recurrence. Recurrence of head and neck HPC has been noted to precede the development of metastasis. Nevertheless, only one HPC in the sinonasal region with appreciable adipose tissue component (LHPC) has been reported. Although it is now obvious that not all head and neck HPCs act in a benign fashion, LHPC is a better actor than its counterpart in the head and neck HPC has been noted to precede the development of metastasis. Nevertheless, only one HPC in the sinonasal region with appreciable adipose tissue component (LHPC) has been reported. Although it is now obvious that not all head and neck HPCs act in a benign fashion, LHPC is a better actor than its counterpart in the soft tissue/axial-skeletal ones.

The results of immunohistochemical analysis in this case are informative. The positive stains of vimentin, CD34, CD99, XIIIa, and Bcl-2 and the negative stains of MSA, desmin, cytokeratin, and CD31 are consistent with previous reports. Diffuse positivity of CD57 in our case provides supportive evidence suggesting LHPC is linked with HPC, because this marker is also present in about 50% of conventional HPC. Moreover, our results suggest that CD57 should be used in the immunohistochemical panel in any lesion suspected to be LHPC. Furthermore, CD57, along with CD34 and XIIIa, positively stains for primitive mesenchymal stem cells, suggesting a bimodal-multimodal differentiation of LHPC.

The very low nuclear proliferation index in our case, as measured by Mib-1, is consistent with the clinically indolent course of this disease. Although the follow-up period is still too short to reach a definitive conclusion, none of the 33 patients, including our case, with follow-up (range, 6–77 months; median, 18 months) developed recurrences, even though some had positive surgical margins. To our knowledge, flow cytometry has not been reported in LHPC. In this report, we found tumor cells were 100% diploid, with SPF being 3.1%. There was a significant positive correlation between nuclear proliferating score and SPF (p < .001, by Spearman analysis). These findings provide molecular evidence indicating a benign nature of LHPC.

The relatively high percentage of tumor cells with p53 positivity was not entirely surprising. One explanation is that increased p53 expression may not indicate gene mutation at all. Accumulation of normal p53 protein has been recently documented in an ultraviolet-irradiation study, in which normal human skin after irradiation demonstrated elevated p53 protein by immunohistochemistry using DO7, the same antibody used in our present study. It has been suggested that normal p53 acts as part of the DNA damage response. Furthermore, some data indicate that not all mutant p53 proteins lose the normal p53 functions. It has been shown that mutant p53 oncoprotein with alteration at codon 248 or codon 273 is capable of performing many of the normal functions of the wild-type p53. In contrast, p53 mutated at codon 141 or 175 loses its gene transactivation capability. Alternatively, positive immunostaining does not always mean gene mutation. In a comprehensive study of p53 mutation and expression, Marchetti and coworkers reported that only 46% of 28 non-small cell lung cancers with strong nuclear staining were shown by polymerase chain reaction single-strand conformation polymorphism (PCR-SSCP) analysis to have p53 mutations. This absence of p53 mutations was further confirmed by direct sequencing of the cDNA-PCR products. Similarly, the concordance between p53 mutation and p53 protein expression was 65% in another study.

In conclusion, the clinicopathologic features of our case were entirely compatible with those of LHPC, which was first described by Nielsen et al in 1995. Although it is difficult to diagnose such a rare tumor, immunohistochemical analysis and flow cytometry are of utmost importance in the diagnosis of LHPC and DNA ploidy analysis.
predicting behavior of this tumor in the head and neck region. More cases of LHPC of the head and neck must be studied to draw definitive conclusions about its distinct behavior and management.

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REFERENCES