Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Clinicopathological features of atypical lipomatous tumors of the laryngopharynx

Huai-yin SHI[†1], Li-xin WEI[1], Hong-tian WANG[2], Lu SUN[1]

([1]*Department of Pathology, Chinese PLA General Hospital, Beijing 100853, China*)

([2]*Department of Otorhinolaryngology, Chinese PLA General Hospital, Beijing 100853, China*)

[†]E-mail: shihuaiyin@sina.com

Received May 2, 2010; Revision accepted Aug. 29, 2010; Crosschecked Nov. 16, 2010

Abstract: Atypical lipomatous tumor (ALT) of the laryngopharynx is rare. Here we report five cases to demonstrate their clinicopathological features. The patients were four males and one female, aged 41 to 69 years (median 53.6 years). All tumors (two in the hypopharynx and three in the larynx) presented as a slowly growing, painless mass. Symptoms included dysphagia (2/5), dysphonia (3/5), and the feeling of a foreign body in the throat (5/5). Tumors were well circumscribed or focally infiltrative, ranging from 2.0 to 5.0 cm (median, 3.4 cm) in size, and microscopically showed the typical features of lipoma-like ALT. Immunohistochemically, tumor cells were stained with S-100, vimentin, murine double minute 2 (MDM-2), and cyclin-dependent kinase 4 (CDK4). Two patients had local tumor recurrences at 6 and 14 months after initial surgery during follow-up. ALT of laryngopharynx is an indolent tumor. Immunohistochemical staining for MDM-2 and CDK4 is helpful in pathological diagnosis.

Key words: Atypical lipomatous tumor (ALT), Laryngopharynx, Immunohistochemistry
doi:10.1631/jzus.B1000164 **Document code:** A **CLC number:** R73

1 Introduction

Liposarcoma is a malignancy of adipocytic cells that occurs mostly in limbs and retroperitoneum. Liposarcoma is classified into four subtypes according to the World Health Organization (WHO) classification of soft tissue tumors (Fletcher *et al.*, 2002), including atypical lipomatous tumor (ALT)/well-differentiated liposarcoma, myxoid/round cell liposarcoma, dedifferentiated liposarcoma, and pleomorphic liposarcoma. ALTs are those well-differentiated liposarcomas located in the superficial parts of the body, and bear a favorable prognosis if completely excised (Fletcher *et al.*, 2002). The proportion of ALT among all liposarcomas is about 40%–45%, and ALTs are further subclassified into three variants, namely the lipoma-like, sclerosing, inflammatory, and spindle cell variants. Liposarcoma of the laryngopharynx is very rare (Wenig *et al.*, 1990; Wenig and Heffner, 1995; Wambeek and Mendelson, 1996; Fahmy *et al.*, 1998; Mestre de Juan and Fernández-Aceñero, 1999; Mouret, 1999; Brauchle *et al.*, 2001; Lippert *et al.*, 2002; Powitzky *et al.*, 2007; Luna-Ortiz *et al.*, 2009). The largest series of laryngopharyngeal liposarcoma is reported by Wenig *et al.* (1990) and Wenig and Heffner (1995), in which ten cases were clinicopathologically analyzed. ALT is the most common variant of liposarcoma in the laryngopharynx (Wenig *et al.*, 1990; Wenig and Heffner, 1995; Mandell *et al.*, 1999). The prognosis of ALT is favorable and local recurrences may occur occasionally, but metastasis of ALT is very rare. In this study, we report five additional ALT cases of the laryngopharynx and their morphological features, immunohistochemical staining profile, and differential diagnosis, as well as follow-up data.

2 Materials and methods

The five ALT cases of the laryngopharynx were from the Department of Pathology, Chinese PLA General Hospital, its two affiliated hospitals, and the consultation files of one author (Dr. Huai-yin SHI). Hematoxylin and eosin (H&E) sections were available for all the five cases and the representative blocks were selected for immunohistochemical staining. Antibodies used in this study included cyclin-dependent kinase 4 (CDK4; DC9-31, 1:400 dilution, Biosource), murine double minute 2 (MDM-2; IF2, 1:200, Invitrogen), S-100 protein (polyclonal, 1:6000, Dako), vimentin (clone V9, 1:50, Dako), and Ki-67 (MIB-1, 1:50, Dako). Positive controls were used for all antibodies in immunohistochemical staining of the tumors. The staining was scored as negative (no tumor cells stained), diffuse (at least 50% tumor cells stained), or focal (less than 50% tumor cells stained). Follow-up data were available for all the five patients.

3 Results

3.1 Clinical and follow-up findings

The clinical features of the patients are summarized in Table 1. The five patients were one female and four males, with an age ranging from 41 to 69 years (median 53.6 years). Two tumors arose at the posterior wall of the hypopharynx and three from the larynx (two from the epiglottis and one from the vestibule). All tumors were surgically removed by pharyngolaryngectomy with supplementary CO_2 laser resection. The period of follow-up was from 26 to 96 months, median 56 months. The follow-up data revealed local recurrences in two cases at 6 and 14 months after initial surgical resection. The other three tumors did not recur during the follow-up. The second surgical resection of the recurrent tumors was performed, with a surgery procedure identical to the first, and the patients were negative for disease thereafter. All the five cases were alive during the follow-up period.

3.2 Gross and microscopical examinations

Grossly, the tumors were yellow or grey-white in color and lobulated on cut surface, with no grossly visible necrosis noted. The tumors were covered by intact squamous mucosa in all cases (Fig. 1). Microscopically, three tumors were well circum scribed, but not encapsulated. Other two tumors were partly well demarcated with focal infiltration of the surrounding soft tissue. The tumors were covered by intact squamous mucosa on one side (Fig. 2a), were lobular in arrangement, and were mainly consisted of adipocytes of different sizes and shapes showing hyperchromatic nuclei (Fig. 2b). Univacuolar and multivacuolar lipoblasts were noted in all tumors (Fig. 2c). Four tumors showed features of lipoma-like ALT, and were intermixed with little sclerosing fibrous tissue. In one case, prominent interstitial sclerosis was in accordance with the diagnosis of sclerosing ALT (Fig. 2d). Mitotic activity was very low and no pathological mitoses were noted in all tumors. Necrosis and dedifferentiation of the tumor cells were absent.

3.3 Immunohistochemical staining

The tumor cells were diffusely stained with vimentin (5/5), S-100 (4/5), MDM-2 (3/5), and CDK4 (3/5) (Fig. 3). Focal positivity for MDM-2 (2/5) and CDK4 (2/5) was noted in two tumors. Ki-67 was focally positive in no more than 5% of tumor cells in all the tumors. The results of immunohistochemical staining are summarized in Table 2.

Table 1 Clinicopathological and follow-up data of the five patients

Case No.	Sex	Age (year)	Tumor site	Size (cm)	Histology	Symptoms	Follow-up (month)	Follow-up data
1	F	45	Vestibule of larynx	3.0	Lipoma-like	Dysphonia	56	NED
2	M	41	Hypopharynx	4.5	Sclerosing	Dysphonia	42	Recur at 6 months
3	M	56	Epiglottis	2.5	Lipoma-like	Dysphagia	60	NED
4	M	58	Hypopharynx	5.0	Lipoma-like	Dysphonia	26	Recur at 14 months
5	M	69	Epiglottis	2.0	Lipoma-like	Dysphagia	96	NED

M: male; F: female; NED: no evidence of disease

Table 2 Immunohistochemical staining results of the five cases

Case No.	Vimentin	S-100	MDM-2	CDK4	Ki-67
1	Diffusely (+)	Diffusely (+)	Focally (+)	Focally (+)	Focally, less than 5%
2	Diffusely (+)	Focally (+)	Diffusely (+)	Focally (+)	Focally, less than 5%
3	Diffusely (+)	Diffusely (+)	Focally (+)	Diffusely (+)	Focally, less than 5%
4	Diffusely (+)	Focally (+)	Diffusely (+)	Diffusely (+)	Focally, less than 5%
5	Diffusely (+)	Diffusely (+)	Diffusely (+)	Diffusely (+)	Focally, less than 5%

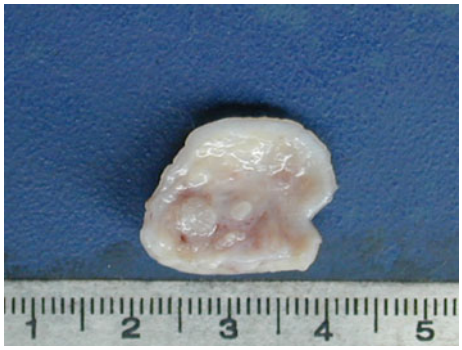

Fig. 1 Gross examination of the tumors
Grossly, the tumors were yellow and grey-white in color and lobulated on the cut surface. The tumors were covered by intact squamous mucosa on one side

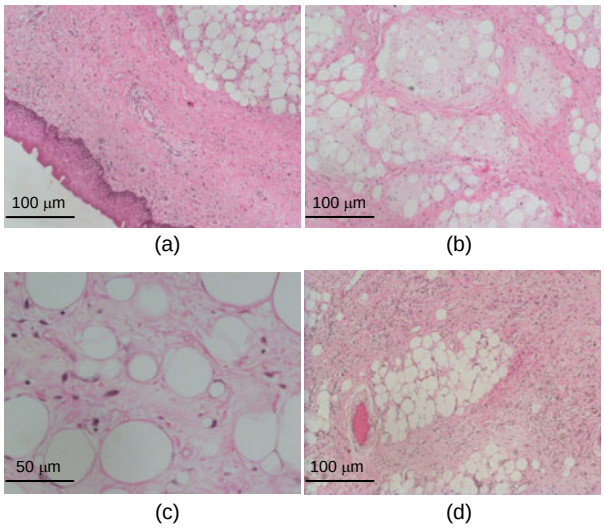

Fig. 2 Microscopical examination of the tumors
The tumors were covered by intact squamous mucosa (H&E) (a), were lobular in arrangement, and were composed of adipocytes of different sizes and shapes showing hyperchromatic nuclei (H&E) (b). Univacuolar and multivacuolar lipoblasts were present in every case (H&E) (c). In one case, prominent interstitial sclerosis and little adipose were in accordance with the diagnosis of sclerosing ALT (H&E) (d)

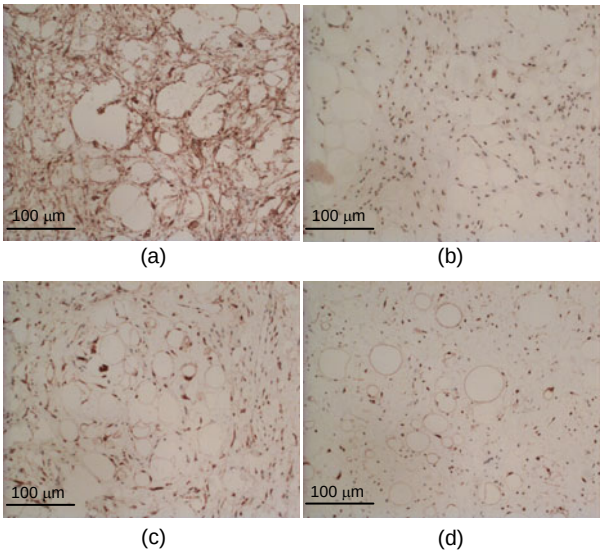

Fig. 3 Immunohistochemical staining of the tumors
The tumor cells stained diffusely or focally with vimentin (a), S-100 (b), MDM-2 (c), and CDK4 (d)

4 Discussion

Liposarcoma, mostly occurring in the retroperitoneum and extremities, is the most common malignant mesenchymal tumor of adulthood. However, its occurrence in the laryngopharynx is relatively rare. Mandell *et al.* (1999) had reviewed 39 cases of liposarcoma of upper aerodigestive tract, among which 26 were located in the larynx, 7 in the hypopharynx, and 6 in the esophagus. These patients had a mean age of 55.8 years, and most of the patients were males. A total of 86% of the tumors in the above-mentioned review were histologically low-grade and only half of them had local recurrence after tumor excision. Distant metastases occurred in only three patients and two patients died of the disease. It was argued that whether or not the tumor had been completely removed seemed to be more closely correlated with the

tumor recurrence than with the histological subtype (Mandell *et al.*, 1999). For anatomical reasons, the extensiveness of surgery for laryngopharyngeal tumors, including ALT, is usually restricted to some extent and the surgical margins are relatively close to the tumor. Thus pharyngolaryngectomy with supplementary laser resection is the optimal choice for laryngopharyngeal ALT in order to remove the tumor as completely as possible. Most laryngopharyngeal liposarcomas are well differentiated, located in the submucosal area, and covered by intact mucosa. They usually have morphological features of lipoma-like subtype, and the sclerosing subtype is only occasionally or focally noted (Wenig *et al.*, 1990; Wenig and Heffner, 1995; Mandell *et al.*, 1999). Other variants of liposarcoma such as myxoid liposarcoma or pleomorphic liposarcoma are very rare in the laryngopharynx. Immunohistochemically, the tumor cells of ALT were permanently labelled with vimentin and S-100 proteins. Other antigens frequently present in ALT include MDM-2, CDK4, and high mobility group protein isoform I-C (HMGI-C) (Xiao *et al.*, 1995; Rogalla *et al.*, 1996; Dei Tos *et al.*, 2000). These antigens are coded by the genes located in 12q13–15, which are present in more than 90% ALT cases (Dal Cin *et al.*, 1993; Fletcher *et al.*, 1996; Rosai *et al.*, 1996; Pedeutour *et al.*, 1999). In this study, we performed immunohistochemical staining of MDM-2 and CDK4 and found that the tumor cells were diffusely or focally positive for these two antigens in all the five cases. Thus, it was concluded that MDM-2 and CDK4 may be useful in the differential diagnosis between lipoma and ALT of the laryngopharynx.

ALT of the laryngopharynx should be differentiated from other benign lipomatous tumors such as classical lipoma, spindle cell lipoma, and pleomorphic lipoma (Arista-Nasr *et al.*, 1998; Jungehülsing *et al.*, 2000; Cantarella *et al.*, 2001; Persaud *et al.*, 2002). However, the adipocytic cells in classical lipoma do not show hyperchromatic nuclei, a typical histological feature of ALT. Otherwise, the adipocytes of lipoma are more uniform in size and shape and lipoblasts are absent. Spindle cell/pleomorphic lipoma (SC/PL), although rare in the laryngopharynx, can occasionally occur (Arista-Nasr *et al.*, 1998; Cantarella *et al.*, 2001). Likewise, SC/PL is usually composed of mature adipose and the size and shape of the adipocytic cells are relatively uniform. In addition, SC/PL is characterized by the presence of thick rope-like collagen bundles, without cells having atypical hyperchromatic nuclei as seen in the ALT, and immunohistochemically the spindle tumor cells are not stained with MDM-2 and CDK4.

Although most ALTs can be diagnosed microscopically based on H&E sections, sometimes it may be difficult to make the differential diagnosis between ALT and lipoma or between ALT and SC/PL. In these cases, immunohistochemical staining of MDM-2 and CDK4 may be very useful as an aid in the differential diagnosis. Considering the indolent biological behavior, we think that ALT is a more suitable term for these laryngopharyngeal tumors than well-differentiated liposarcoma in order to avoid excessive treatment.

5 Conclusions

Most ALTs of the laryngopharynx can be cured by complete excision of the tumors; however, incomplete excision of the tumor may result in local recurrence. Immunohistochemical staining for MDM-2 and CDK4 is helpful in the pathological diagnosis.

6 Acknowledgements

The authors thank En-ping BA, Wei CHEN, Xin SONG, and Ling-hong CHEN (technicians of Department of Pathology, Chinese PLA General Hospital) for their technical assistance.

References

Arista-Nasr, J., Tapia, B., Rodriguez-Ribero, D., Magallon-Sesma, V., Hernandez, J., 1998. A case of pleomorphic lipoma of the hypopharynx. *Rev. Invest. Clin.*, **50**(3): 259-261.

Brauchle, R.W., Farhood, A.I., Pereira, K.D., 2001. Well-differentiated liposarcoma of the epiglottis. *J. Laryngol. Otol.*, **115**(7):593-595. [doi:10.1258/0022215011908342]

Cantarella, G., Neglia, C.B., Civelli, E., Roncoroni, L., Radice, F., 2001. Spindle cell lipoma of the hypopharynx. *Dysphagia*, **16**(3):224-227. [doi:10.1007/s00455-001-0066-8]

Dal Cin, P., Kools, P., Sciot, R., de Wever, I., van Damme, B., van de Ven, W., van den Berghe, H., 1993. Cytogenetic and fluorescence in situ hybridization investigation of ring chromosomes characterizing a specific pathologic subgroup of adipose tissue tumors. *Cancer Genet. Cytogenet*, **68**(2):85-90. [doi:10.1016/0165-4608(93)90001-3]

Dei Tos, A.P., Doglioni, C., Piccinin, S., Sciot, R., Furlanetto, A., Boiocchi, M., Dal Cin, P., Maestro, R., Fletcher, C.D., Tallini, G., 2000. Coordinated expression and amplification of the *MDM2*, *CDK4*, and *HMGI-C* genes in atypical lipomatous tumours. *J. Pathol.*, **190**(5):531-536. [doi:10.1002/(SICI)1096-9896(200004)190:5<531::AID-PATH579>3.3.CO;2-N]

Fahmy, F.F., Osborne, J., Khalil, H.S., Rodgers, B., 1998. Well-differentiated liposarcoma of the hypopharynx. *J. Laryngol. Otol.*, **112**(9):880-882. [doi:10.1017/S0022215100141969]

Fletcher, C.D., Akerman, M., Dal Cin, P., de Wever, I., Mandahl, N., Mertens, F., Mitelman, F., Rosai, J., Rydholm, A., Sciot, R., *et al*., 1996. Correlation between clinicopathological features and karyotype in lipomatous tumors. A report of 178 cases from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. *Am. J. Pathol.*, **148**(2):623-630.

Fletcher, C.D.M., Nielsen, G.P., Mandahl, N., Dei Tos, A.P., Miettinen, M.M., Pedeutour, F., 2002. Adipocytic Tumours. *In*: Fletcher, C.D.M., Unni, K.K., Mertens, F., (Eds.), WHO Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone, 1st Ed. IARC, Lyon, p.19-46.

Jungehülsing, M., Fischbach, R., Pototschnig, C., Eckel, H.E., Damm, M., 2000. Rare benign tumors: laryngeal and hypopharyngeal lipomata. *Ann. Otol. Rhinol. Laryngol.*, **109**(3):301-305.

Lippert, B.M., Eggers, S., Schlüter, E., Rudert, H., Werner, J.A., 2002. Lipoma of the larynx. Report of 2 cases and review of the literature. *Otolaryngol. Pol.*, **56**(6):669-674.

Luna-Ortiz, K., Campos-Ramos, E., Carmona-Luna, T., Mohar-Betancourt, A., Ferrari-Carballo, T., 2009. Laser resection of liposarcoma of the hypopharynx. *Med. Oral. Patol. Oral. Cir. Bucal.*, **14**(5):E252-E256.

Mandell, D.L., Brandwein, M.S., Woo, P., Som, P.M., Biller, H.F., Urken, M.L., 1999. Upper aerodigestive tract liposarcoma: report on four cases and literature review. *Laryngoscope*, **109**(8):1245-1252. [doi:10.1097/00005537-199908000-00012]

Mestre de Juan, M.J., Fernández-Aceñero, M.J., 1999. Laryngeal liposarcoma: report of a case. *Pathol. Res. Pract.*, **195**(2):125-128.

Mouret, P., 1999. Liposarcoma of the hypopharynx. A case report and review of the literature. *Rev. Laryngol. Otol. Rhinol. (Bord.)*, **120**(1):39-42.

Pedeutour, F., Forus, A., Coindre, J.M., Berner, J.M., Nicolo, G., Michiels, J.F., Terrier, P., Ranchere-Vince, D., Collin, F., Myklebost, O., *et al*., 1999. Structure of the supernumerary ring and giant rod chromosomes in adipose tissue tumors. *Genes Chromosomes Cancer*, **24**(1):30-41. [doi:10.1002/(SICI)1098-2264(199901)24:1<30::AID-GCC5>3.0.CO;2-P]

Persaud, R.A., Kotnis, R., Ong, C.C., Bowdler, D.A., 2002. A rare case of a pedunculated lipoma in the pharynx. *Emerg. Med. J.*, **19**(3):275. [doi:10.1136/emj.19.3.275]

Powitzky, R., Powitzky, E.S., Garcia, R., 2007. Liposarcoma of the larynx. *Ann. Otol. Rhinol. Laryngol.*, **116**(6):418-424.

Rogalla, P., Drechsler, K., Frey, G., Hennig, Y., Helmke, B., Bonk, U., Bullerdiek, J., 1996. HMGI-C expression patterns in human tissues. Implication for the genesis of frequent mesenchymal tumors. *Am. J. Pathol*, **149**(3):775-779.

Rosai, J., Akerman, M., Dal Cin, P., de Wever, I., Fletcher, C.D., Mandahl, N., Mertens, F., Mitelman, F., Rydholm, A., Sciot, R., 1996. Combined morphologic and karyotypic study of 59 atypical lipomatous tumors. Evaluation of their relationship and differential diagnosis with other adipose tissue tumors (a report of the CHAMP Study Group). *Am. J. Surg. Pathol.*, **20**(10):1182-1189. [doi:10.1097/00000478-199610000-00002]

Wambeek, N.D., Mendelson, R.M., 1996. Liposarcoma of the hypopharynx. *Australas. Radiol.*, **40**(2):165-168. [doi:10.1111/j.1440-1673.1996.tb00375.x]

Wenig, B.M., Heffner, D.K., 1995. Liposarcomas of the larynx and hypopharynx: a clinicopathologic study of eight new cases and a review of the literature. *Laryngoscope*, **105**(7):747-756. [doi:10.1288/00005537-199507000-00013]

Wenig, B.M., Weiss, S.W., Gnepp, D.R., 1990. Laryngeal and hypopharyngeal liposarcoma. A clinicopathologic study of 10 cases with a comparison to soft-tissue counterparts. *Am. J. Surg. Pathol.*, **14**(2):134-141. [doi:10.1097/00000478-199002000-00005]

Xiao, Z.X., Chen, J., Levine, A.J., Modjtahedi, N., Xing, J., Sellers, W.R., Livingston, D.M., 1995. Interaction between the retinoblastoma protein and the oncoprotein MDM2. *Nature*, **375**(6533):694-697. [doi:10.1038/375694a0]