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CLINICAL REVIEW

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Epstein–Barr virus-associated leiomyosarcoma of the larynx in an adult patient with human immunodeficiency virus infection: Case report and review of the literature

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Abstract

We investigated the clinical features, treatment, and prognosis of laryngeal leiomyosarcoma (LLMS) and Epstein–Barr virus-associated (EBV-associated) LMS. We report a case of EBV-associated LLMS in an adult patient with HIV infection. We also conducted a review of the English-language literature on LLMS and EBV-associated leiomyosarcoma. To the best of our knowledge, 62 cases of LLMS and EBV-associated leiomyosarcoma have been reported to date. Of patients with LLS, 18.9% had distant metastases and 17.0% had local recurrence. The overall 5-year survival rate was 64.0%. Distant metastases affected the survival of patients with LLMS ($p = 0.04$). EBV-positive patients had a low survival rate ($p = 0.01$). Among patients with EBV-associated LMS, 8.2% had distant metastases and recurrence and the overall 5-year survival rate was 50.0%. EBV-associated LLMS is rare. The EBV infection might be a poor prognostic factor of LLMS.

KEYWORDS

Epstein-Barr virus-associated leiomyosarcoma, laryngeal leiomyosarcoma, prognosis, recurrence, treatment

1 | INTRODUCTION

Laryngeal leiomyosarcoma (LLMS) is uncommon. It constitutes approximately 7.4% of all LMS cases.[1] It was first reported by Jackson and Jackson in 1939.[2] To the best of our knowledge, 62 cases of LLMS have been reported in the English-language literature.[1,3–55]

Factors predisposing to LLMS include radiation exposure, surgery, multiple basal cell carcinoma syndrome, Gardner syndrome, tuberous sclerosis, neurofibromatosis, Werner syndrome, retinoblastoma, Turcot syndrome, and Epstein–Barr virus (EBV) infection in immunosuppressed patients.[1,3–55]

Several cases of EBV-related LMS in immunosuppressed patients have been reported.[25,29,39,56–98] LMS in immunosuppressed patients after organ transplantation and in patients with human immunodeficiency virus (HIV) is associated with EBV. EBV-associated LMS is common in children with HIV, and uncommon in adult patients with HIV.[25,29,39,56–98] Marioni et al.[19] reported

LLMS in a patient with two kidney transplants. They detected EBV in LMS tissues but not neoplastic tissues. To date, only three cases of LLMS related to EBV infection have been reported.[25,29,39]

We report a case of EBV-related LLMS in an adult patient with HIV infection. We also reviewed cases of LLMS and EBV-related LMS by searching the MEDLINE and EMBASE databases, and analyzed their clinical features, treatment, and prognosis.

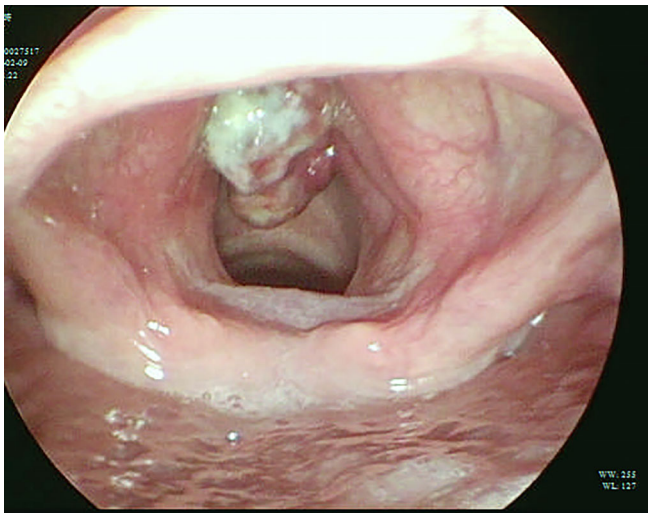

FIGURE 1 Laryngoscopy showed a mass in the anterior commissure of the vocal cord [Color figure can be viewed at wileyonlinelibrary.com]

2 | CASE REPORT

A 20-year-old male with a 7-month history of hoarseness presented to the Department of Otolaryngology of our hospital. Laryngoscopy showed a mass in the anterior commissure of the vocal cords (Figure 1). During hospitalization, he was determined to be HIV positive and received antiretroviral therapy (lamivudine 300 mg plus efavirenz 600 mg plus tenofovir fumarate 300 mg QD) for 6 months. The EBV-DNA serum level was high (5.56×10^4 copies/mL; normal, <500 copies/mL).

The patient was transferred to the Department of Infection. There were no complaints of difficulty breathing or dysphagia. He was a non-smoker and not an alcoholic. He had no cervical lymphadenopathy. Rigid laryngoscopy showed a 0.5 × 1.0 cm mass located at the anterior commissure covering the bilateral vocal cord and subglottic extension. The mobility of both vocal cords was normal. MRI of the larynx showed a 1.0 × 1.1 cm mass at the anterior commissure. The mass was hyperintense in T1 images, hyperintense in T2 images, hyperintense in diffusion-weight imaging (DWI), and showed strong contrast enhancement. The paraglottic and

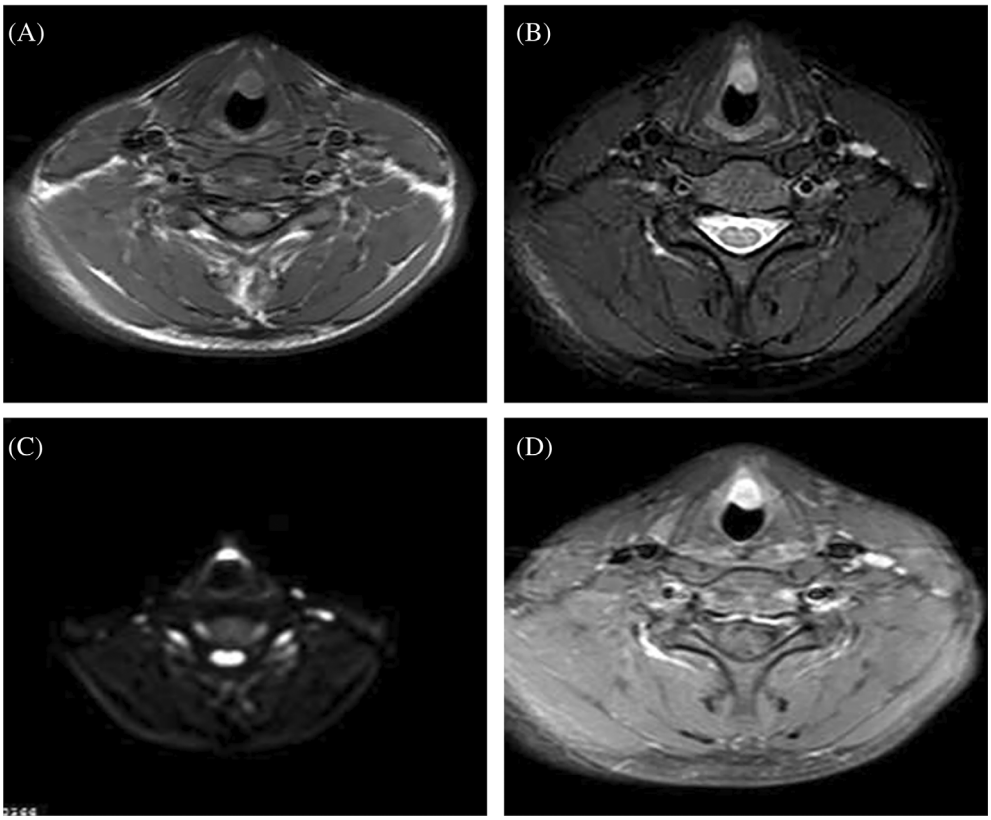

FIGURE 2 MRI of the larynx showed a 1.0 × 1.1 cm mass at the anterior commissure (arrow). The mass was hyperintense in T1 images (A), T2 images (B), and DWI (C), and showed strong contrast enhancement (D)

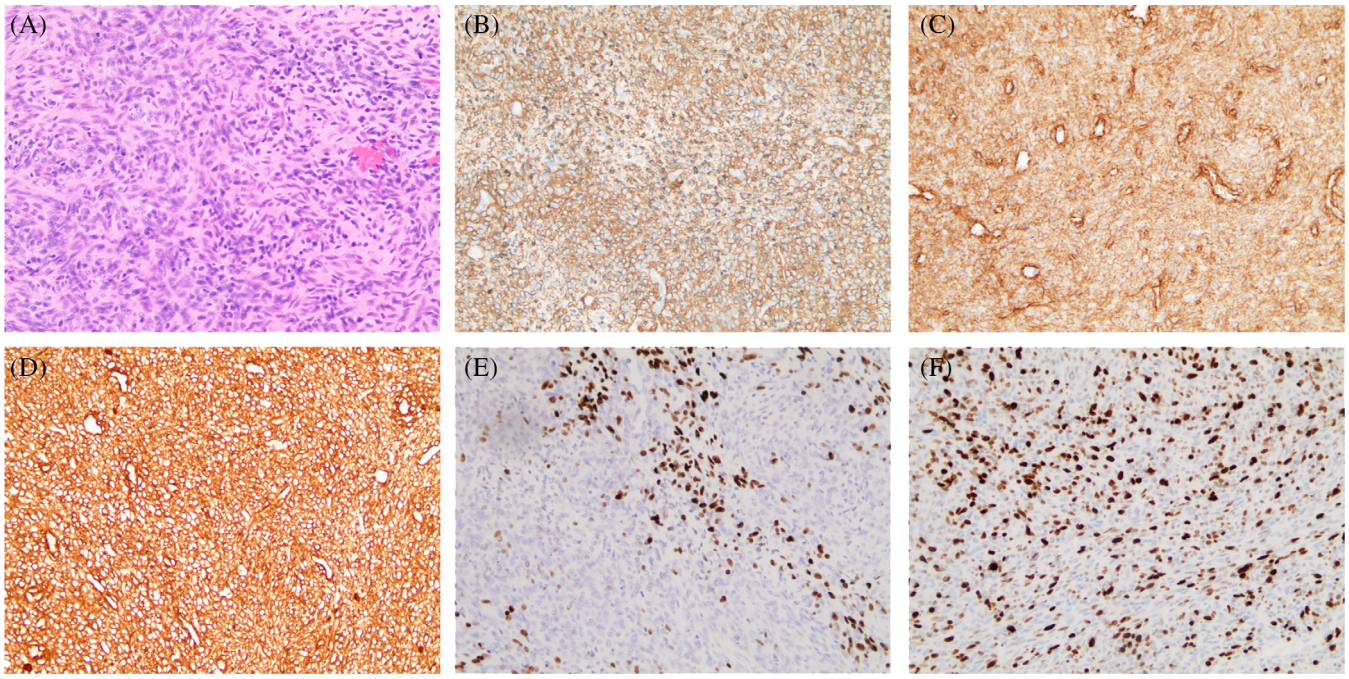

FIGURE 3 Postoperative pathological results showed proliferation of spindle-shaped cells arranged in solid bundles with infiltrating growth (A, hematoxylin and eosin; original magnification, ×20). Immunohistochemical analysis showed that the tumor cells were positive for SMA (B, ×20), β-catenin (C, ×20), and caldesmon (D, ×20). Tumor cells were EBER positive in ISH (E, ×20). The Ki-67 positivity rate was 40% (F) [Color figure can be viewed at wileyonlinelibrary.com]

pre-epiglottic spaces were clear (Figure 2). Thereafter, microlaryngosurgery was performed under general anesthesia and the exposed tumor was a 0.5 × 1.0 cm mass at the anterior commissure covering the bilateral vocal cords and subglottic extension. The postoperative pathological results showed proliferation of spindle-shaped cells arranged in solid bundles with infiltrating growth. There were 10 mitoses per 10 high-power fields. The mitotic rate was >10 per field. Immunohistochemical analysis showed that the tumor cells were positive for smooth muscle actin (SMA), β-catenin, caldesmon, and CD99 (Figure 3) and negative for CK (pan), S-100, desmin, CD3, CD31, ERG, HHV8, SOX10, STAT6, and MyoD1. Tumor cells were positive for Epstein–Barr early RNA in in situ hybridization (ISH) analyses. The Ki-67 positivity rate was 40%. According to the eighth version of the AJCC T/N/M classification for laryngeal cancer, the T/N/M classification of LLMS was $T_{1b}N_0M_0$ and TNM stage I.

The patient underwent CO_2 laser resection by microlaryngeal surgery under general anesthesia. The tumor was completely resected, and with clear surgical margins. Postoperative recovery was uneventful, and the patient was discharged the next postoperative day. After 2 months of follow-up, no further recurrence or metastasis were noted.

This study was approved by the Institutional Review Board of The First Affiliated Hospital, College of Medicine, Zhejiang University, China.

3 | DISCUSSION/LITERATURE REVIEW

3.1 | Clinical features of laryngeal leiomyosarcoma

LLMS is uncommon; we identified 62 cases in the English-language literature (Table 1).[1,3–55] Tangjaturonrasme found that the number of LLMS cases was increasing; four cases were reported from 1961 to 1970, compared to 21 cases from 2000 to 2010. This may be a result of advances in diagnostic techniques, including immunohistochemical techniques and electron microscopy.[46] We found 21 cases from 2000 to 2010 and 21 from 2011 to 2021.

Among the 62 LLMS cases, 61 had complete clinical details. There were 55 males (90.2%) and 6 females (9.8%); the male-to-female ratio was approximately 9:1. The patients ranged in age from 10 to 85 years at initial presentation, with a mean age of 59.1 years. The results were similar to a prior report.[36] Among the 61 patients for whom age data were available, 4 patients (6.6%) were <30 years old, 5 (8.2%) were 30–39 years old, 10 (16.4%) were 40–49 years old, 24 (39.3%) were 50–69 years old, 10 (16.4%) were 70–79 years old, and 8 patients (13.1%) were ≥80 years old. Most patients (68.8%) were >50 years old, unlike the report by Paczona et al.[15] Reyes et al.[25]

TABLE 1 Review of English-literature of laryngeal leiomyosarcoma

No. of patients	Year/author/ref.	Age/sex	Chief complaint	Site	Treatment, recurrence, metastasis and outcome
1	1947/Eggston[3]	M/40	Hoarseness, dyspnea	Glottis	TL, ND after 18 months, no recurrence and metastasis
2	1973/Woflwitz[4]	M/40	Hoarseness, dyspnea	Glottis	Laryngectomy, ND after 18 months, no recurrence and metastasis
3	1973/Woflwitz[4]	M/40	Hoarseness, dyspnea and choking feeling	Supraglottis	Excision, ND after 6 months, no recurrence and metastasis
4	1979/Kleinsasser[5]	M/60	Hoarseness	Transglottis	RT, died after 31 months, recurrence after 1 year, only agree to an endoscopic remove, laryngectomy after following year, multiple metastases after 28 months appeared in the neck, in the lungs, bone marrow, liver, adrenal glands, colon, spleen, heart, and thyroid gland
5	1979/Kleinsasser[5]	M/35	Hoarseness	Supraglottis	HL + RT(50 Gy). The first recurrence after 3 months, a laryngectomy + RT (50 Gy). Another recurrence in the region of the hyoid bone after 6 months, resected. 9 months later, the third recurrence: resection of the entire skin of the anterior side of the neck, the root of the tongue, the whole pharynx and the anterior half of the right carotid bulb which was infiltrated by the tumor was carried out in a last-ditch attempt to control a rapidly growing recurrence. The carotid artery was sutured, the pharynx was reconstructed with fascia lata, and the skin defect was closed with a large deltopectoral flap. The patient sometimes has to dilate his narrow pharynx himself, but he has even learned understandable pharyngeal speech and has otherwise been healthy now for 14 years.
6	1986/Levine[6]	F/28	Hoarseness, dyspnea	Supraglottis	Surgical excision + RT, ND after 18 months, no recurrence and metastasis
7	1991/Chen[7]	M/69	Hoarseness, stridor	Supraglottis	HL-END-RT, ND after 18 months, no recurrence and metastasis
8	1991/Tewary[8]	M/56	Anxious and had inspiratory stridor	Glottis	TL, alive 41 months, no recurrence and metastasis
9	1994/Rowe-Jones[9]	M/87	Dysphonia	Glottis	CO_2 laser + RT, ND after 3 months, no recurrence and metastasis
10	1995/McKiernan[10]	M/43	Hoarseness	Supraglottis	CO_2 laser + supraglottic partial laryngectomy + RT, ND after 6 months, no recurrence and metastasis
11	1996/Helmberger[11]	M/87	Hoarseness shortness of breath, dysphagia, and right-sided otalgia	Glottis	TL, ND after 30 months, no recurrence and metastasis
12	1997/Lippert[12]	M/50	Hoarseness	Glottis	CO_2 laser, ND after 25 months, no recurrence and metastasis
13	1998/Sindwani[13]	M/38	Intermittent oropharyngeal dysphagia	Supraglottis	lateral pharyngotomy + postoperative RT, alive after 25 months, lung metastasis
14	1999/Cocks[14]	M/49	Hoarseness	Glottis	Tracheostomy + TL and total thyroidectomy + RT, 25 months alive, multiple lung metastasis after 25 months

(Continues)

TABLE 1 (Continued)

No. of patients	Year/author/ref.	Age/sex	Chief complaint	Site	Treatment, recurrence, metastasis and outcome
15	1999/Cocks[14]	M/79	Hoarseness	Glottis	The tumor at the time of biopsy was completely removed, ND after 22 months, no recurrence and metastasis
16	1999/Paczona[15]	M/65	Hoarseness	Glottis	Hyperkeratosis and mild dysplasia CO_2 laser, 1.5 year later, laryngeal leiomyosarcoma, TL + ND, ND after 4 years, no recurrence and metastasis
17	1999/Paczona[15]	F/31	Hoarseness	Glottis	CO_2, ND after 22 months, no recurrence and metastasis
18	1999/Thomas[16]	M/72	Shortness of breath hoarseness, stridor, and a foreign body sensation in his throat	Subglottis	TL, ND after 5 years, no recurrence and metastasis
19	1999/Yoshizaki[17]	F/81	Stridor, aspiration both inspiratory and expiratory	Glottis	Tracheotomy + TL, ND after 6 months, no recurrence and metastasis
20	1999/Chae[18]	M/64	Stridor	Glottis	HL, ND after 36 months, no recurrence and metastasis
21	2000/Marioni[19]	M/41	Dysphonia	Glottis	Completely removed under microlaryngoscopy + postoperative RT, 13 months later, metastasis in lung and thyroid glands. Died after 15 months
22	2000/Wadhwa[20]	M/62	Hoarseness	Glottis	TL + hemithyroidectomy, ND after 11 years
23	2001/Kainuma[21]	M/79	Stridor and dysphagia	Glottis	TL + postoperative RT, died after 9 months
24	2001/Lan[22]	M/68	Hoarseness	Glottis	NA
25	2002/Ingen-Housz-Oro[23]	M/78	Dysphonia	Glottis	Total laryngectomy + bilateral, died after 6 months recurrence involving the posterior tracheal wall treated with cyclophosphamide 100 mg orally per day
26	2002/Fusconi[24]	M/69	Dyspnea	Glottis	CO_2 laser, ND after 23 months, no recurrence and metastasis
27	2002/Reyes[25]	F/10	Rapid onset of respiratory distress	Supraglottis	Right partial supraglottic laryngectomy, ND after 9 months, no recurrence and metastasis
28	2003/Preti[26]	M/50	Serious dyspnea	Supraglottis	Partial laryngectomy + postoperative RT, alive after 6 months, 6 months later, metastasis in lung
29	2004/Sasaki[27]	M/62	Hoarseness	Subglottis	TL, ND after 5 years, no recurrence and metastasis
30	2005/Akcam[28]	M/47	Hoarseness, stridor and dysphagia	Glottis	TL-END bilateral, ND after 12 months, no recurrence and metastasis
31	2005/Suankratay[29]	M/32	Hoarseness	Glottis	Total mass removal, ND after 3 months, no recurrence and metastasis
32	2005/Marioni[30]	M/56	Dysphonia	Glottis	Surgical excision of the glottic lesion was performed under microlaryngoscopic control, 4 months later, recurrence, CO_2 laser cordectomy; 5 months later, another recurrence, another surgical procedure under microlaryngoscopic control. ND after 5 months

TABLE 1 (Continued)

No. of patients	Year/author/ref.	Age/sex	Chief complaint	Site	Treatment, recurrence, metastasis and outcome
33	2005/Abbas[31]	M/65	Hoarseness, breathing difficulty	Glottis	Emergency tracheotomy + total laryngectomy, ND after 12 months, no recurrence and metastasis
34	2005/Darouassi[32]	F/48	Hoarseness	Glottis	TL + total thyroidectomy, ND after 5 months, no recurrence and metastasis
35	2006/Skoulakis[33]	M/74	Progressive hoarseness.	Glottis	Emergency tracheotomy + TL, 8 months lung metastasis, died after 11 months
36	2006/Rimmer[34]	M/69	Hoarseness	Glottis	Excised through microlaryngosopy + postoperative RT, ND after 6 months, no recurrence and metastasis
37	2007/Gupta[35]	M/70	Stridor, hoarseness	Glottis	Emergent tracheostomy + TL + postoperative radiotherapy, ND after 12 months, no recurrence and metastasis
38	2008/Goda[36]	M/65	Hoarseness, breathlessness stridor	Supraglottis	TL with partial pharyngectomy and hemithyroidectomy + postoperative RT, ND after 35 months, no recurrence and metastasis
39	2009/Tomidokoro[37]	M/74	Hoarseness	Glottis	Partial laryngectomy (fronto-lateral), ND after 9 months, no recurrence and metastasis
40	2010/Völker[38]	M/85	Acute dyspnea, inspiratory stridor progressive during the previous 4 weeks	Glottis	A complete laser resection, ND after 16 months, no recurrence and metastasis
41	2010/Huang[39]	M/54	Progressively worsening stridor	Glottis	TL, died after 8 months
42	2013/Yadav[40]	NA	Hoarseness	NA	NA
43	2013/Khadivi[41]	M/49	Severe respiratory distress, odynophagia and dysphagia which were associated with biphasic stridor. The respiratory distress had begun 1 week ago	Supraglottis	NA
44	2013/Thomas[42]	M/60	Dysphonia	Subglottis	TL + partial pharyngectomy with bilateral neck dissection and postoperative RT. 6 years metastasis to left axillary mass. The patient underwent surgical resection of both lesions. Alive, 6 years
45	2013/Singh[43]	M/63	Hoarseness, breathlessness, stridor, dysphagia	Glottis	Emergency tracheostomy + TL + RT. ND after 6 months, no recurrence and metastasis
46	2013/Kara[44]	M/50	Hoarseness	Glottis	CO_2 laser resection, ND after 36 months, no recurrence and metastasis
47	2013/Kara[44]	M/55	Dyspnea, hoarseness	Glottis	TL, right lateral neck dissection and right total thyroid lobectomy were performed. ND after 15 months, no recurrence and metastasis

(Continues)

TABLE 1 (Continued)

No. of patients	Year/author/ref.	Age/sex	Chief complaint	Site	Treatment, recurrence, metastasis and outcome
48	2015/Selçuk[45]	M/82	Shortness of breath, hoarseness	Glottis	NA
49	2015/ Tangjaturonrasme[46]	M/68	Hoarseness, breathing difficulty	Supraglottis	Emergency tracheostomy + TL + RT, ND after 5 months, no recurrence and metastasis
50	2016/Ismi[47]	M/42	Respiratory distress	Subglottis	Emergency tracheotomy + extended TL: strap muscles, thyroid gland, and left internal jugular vein with left modified radical neck dissection was performed. Right modified radical neck dissection was performed 6 weeks later. 1 month lung metastasis. Alive, 1 month
51	2018/AbdullGaffar[48]	M/74	Change of voice	Glottis	NA
52	2019/Saraydaroglu[49]	F/66	Dysphonia	Glottis	NA
53	2019/Saraydaroglu[50]	M/84	Respiratory distress	Glottis	NA
54	2019/NG[49]	M/52	Hoarseness	Glottis	TL. ND after 12 months, no recurrence and metastasis
55	2020/Dorobisz[51]	M/75	Recurrent sore throat, hoarseness, difficult swallowing and dyspnea	Transglottis	NA
56	2020/Molteni[52]	M/84	Dysphonia	Glottis	TL. Alive after 3 months, metastasis in lung
57	2020/Crotty[53]	M/35	Stridor, dysphagia, hoarseness	Glottis	Emergency tracheostomy + chemotherapy (mesna, doxorubicin, ifosfamide and dacarbazine) + RT (60 Gy in 30 fractions) + pharyngolaryngo-esophagectomy (PLO), total thyroidectomy and bilateral-modified radical neck dissection with formation of a neoesophagus from an interpositional jejunal free-flap was performed. Metastasis in hepatic and pulmonary after 6 weeks, died after 10 months
58	2021/Salama[54]	M/50	Hoarseness	Glottis	CO_2 alive, 38 months. 14 months recurrence: TL, bilateral functional neck dissection + postoperative RT
59	2021/Velez Torres[1]	M/65	Difficulty swallowing	Subglottis	TL, partial pharyngectomy, and partial thyroidectomy. Recurrence: 13 months after resection. Died after 48 months.
60	2021/Velez Torres[1]	M/81	Shortness of breath	Supraglottis	NA
61	2021/Cooper[55]	M/77	Hoarseness	Supraglottis	TL + RT. ND after 3.5 years, no recurrence and metastasis
62	Present case	M/20	Hoarseness	Glottis	CO_2. ND after 3 months, no recurrence and metastasis

Note: ND, neck dissection; RT, radiotherapy; HL, hemilaryngectomy; END, elective ND; TL, total laryngectomy; NA, not available.

reported a case of LLMS in a 10-year-old girl, the youngest patient documented in the English-language literature.

LLMS originated from or involved the following regions: 41 of 61 (67.2%) the glottis, 13 of 61 (21.3%) the supraglottis, 5 of 61 (8.2%) the subglottis, and 2 of 61 (3.3%) the transglottis. The clinical symptoms of LLMS depended on its size, site, extent, and surrounding structures.[36] We found that 22 of 61 patients (36.1%) had hoarseness as the sole symptom, 8 of 61 (13.1%) had dysphonia, 5 of 61 (8.2%) had dyspnea, 3 of 61 (4.9%) had stridor, and 1 of 61 (1.6%) had difficulty swallowing. Most patients had overlapping presentations: 8 of 61 (13.1%) had hoarseness and dyspnea, and 14 of 61 (23.0%) had hoarseness/stridor/dyspnea/dysphagia. Ten of sixty-one patients (16.4%) had emergency tracheostomy for serious dyspnea.[14,17,28,33,35,39,43,46,47,53] The laryngoscopic manifestations of LLMS are diverse. It may be limited to the glottis or cover the laryngeal cavity. It may be an ulceroproliferative mass, a prolapsing exophytic tumor, a rounded mass with smooth surface, a pedunculated large glottic lesion, an irregular mass, a polypoid lesion, or a small, smooth submucosal lesion. Only two cases (3.3%) had neck lymph node metastasis.[14,54] The finding in the present case was an irregular mass at the anterior commissure covering the bilateral vocal cords and subglottic extension.

CT and MRI for LLMS can confirm the content and size of the tumor, its relationship with surrounding structures, and neck lymph node metastasis. In CT, the tumor may show heterogeneous enhancement. In MRI, the tumor is hyperintense in T1 images hyperintense in T2 images, hyperintense in DWI, and showed strong contrast enhancement.

3.1.1 | Pathogenesis

The low incidence of LLMS is caused by the scarcity of smooth muscle in the larynx. In the larynx, only blood vessels have smooth muscle tissue, and tumors typically develop from smooth muscle in the tunica media of vessel walls. There are five competing hypotheses on the pathogenesis of LLMS.[15,44,47,53,99,100] It can develop primarily from smooth muscle in the tunica media of vessel walls. Metastases from LMS in other sites can invade the larynx. LLMS may be from aberrant differentiation of mesenchymal tissue in the larynx. It may arise from squamous epithelium by divergent differentiation into mesenchymal cells; that is, rhabdomyoblastic differentiation. Although rhabdomyoblastic differentiation in the larynx is rare, it is common in other organs of the upper respiratory tract. Among 61 cases of LLMS, 5 (8.2%) had simultaneous LLMS and squamous cell carcinoma (SCC).[37,44,51,53,55] One patient had been treated for laryngeal SCC 15 years prior. Synchronous malignant LMS and SCC of the respiratory system may result from sarcoma originating from complete or incomplete mesenchymal metaplasia of the neoplastic tumor.[51] Both synchronous tumors express the same antigens[101] or the same p53 mutations.[102,103]

Aberrant differentiation after healing of surgical trauma may be an alternative pathway in the pathogenesis of LLMS. Tissue trauma including surgery may be a risk factor for head-and-neck sarcoma.[38,41,47,104] Dijkstra et al.[104] reported that 5 of 60 head-and-neck sarcomas had a history of surgery at the site of sarcoma; 2 were LMS. Among 61 patients with LLMS, 3 were diagnosed after treatment for metachronous laryngeal SCC.[38,41,47] One received CO_2 laser microsurgery and the others underwent total laryngectomy.[38] Völker et al.[38] suggested that surgical trauma might lead to aberrant differentiation and LLMS.

Fusconi et al.[24] proposed that LLMS might develop from residual stem cells of macula flava, which could be mesenchymal or stromal stem cells in bone marrow.[105,106] These can differentiate into smooth muscle cells.[105,106]

3.1.2 | Predisposing factors

Unlike SCC, LMS is not strongly associated with a history of smoking. In this review, only 27 articles provided a history of smoking and alcohol use. Twelve patients (44.4%) had no history of smoking or alcohol consumption, seven patients (25.9%) had a history of both smoking and drinking, and eight patients (29.7%) had a history of smoking but no alcohol consumption.

Predisposing factors of LMS include radiation exposure, surgery,[38,41,47,51] multiple basal cell carcinoma syndrome,[107] Gardner syndrome,[108] tuberous sclerosis,[109] neurofibromatosis,[110] retinoblastoma,[111] Turcot syndrome,[112] and EBV infection in immunosuppressed patients.[13] Most of the 60 patients with LLMS, however, had no past medical history.

In some cases, a history of immunosuppression may predispose to LMS, such as HIV infection,[29,62,64,65,67–69,72,75,76,82,86,87,90,93,94,96,97] post-transplantation,[58,60,61,66,71,73,74,77,79,80,83–85,91,92,95] and EBV. Marioni et al.[19] reported one patient with LLMS who had received two kidney transplants; the patient was negative for EBV in PCR and Southern blotting.

Chromosomal breakage syndrome is a risk factor for developing malignant tumors.[113,114] Reyes et al.[25] first detected EBV positivity in LMS patients. They reported a

TABLE 2 Review of English-literature of EBV-associated leiomyosarcoma

No. of patients	Year/author/ref.	Age/sex	Site	Immune status	Treatment, recurrence, metastasis and outcome
1	1976/Shen[56]	M/5	Kidney	Acute lymphoblastic leukemia	Chemotherapy, no recurrence and metastasis, 9 months alive
2	1995/Zetler[57]	M/30	Adrenal gland	HIV	Surgery, no recurrence and metastasis, 20 months alive
3	1995/Timmons[58]	F/12	The small intestinal mesentery, no multiple lesions	Liver transplantation, 5 years	Surgery, no recurrence and metastasis, 24 months alive
4	1995/Timmons[58]	M/9	Liver, multiple lesions	Liver transplantation, 2 years	Chemotherapy, no recurrence and metastasis, 6 months dead
5	1995/McClain[59]	F/8	Lung	HIV, 4 years	NA
6	1995/McClain[59]	F/4	Stomach	HIV, 2 years	NA
7	1995/McClain[59]	F/7	Intestine	HIV, 2 years	NA
8	1995/McClain[59]	M/24	Liver	HIV, 18 years	NA
9	1995/McClain[59]	F/5	Colon	HIV, 1 year	NA
10	1996/Sadahira[60]	F/21	Liver, multiple lesions	Kidney transplantation, 5 years	No treatment, dead, diagnosed by autopsy
11	1996/Le Bail[61]	F/53	Liver, spleen, multiple lesions	Kidney transplantation, 4 years	NA
12	1997/Morgello[62]	M/35	Dura	HIV	Surgery, no recurrence and metastasis, died after 4 days surgery
13	1997/Mierau[63]	F/14	Transverse sigmoid sinus	Genetic common variable immunodeficiency syndrome	Surgery, no recurrence and metastasis, 21 months alive
14	1997/Jenson[64]	F/29	Thoracic spine with multifocal recurrences	HIV, 27 years	NA
15	1997/Jenson[64]	F/7	Ethmoid sinus and caecum	HIV, 1 year	NA
16	1997/Boman[65]	M/48	Multiple lymph nodes, adrenal gland, pericardium	HIV	Chemotherapy, no recurrence and metastasis, 12 months dead
17	1997/Boman[65]	M/29	Adrenal gland	HIV	No treatment, no recurrence and metastasis, 6 months dead, diagnosed by autopsy
18	1998/Somers[66]	M/15	Lung, liver, multiple lesions	Heart, kidney, 3 years	Reduced immunosuppression, antiviral drug, no recurrence and metastasis, 38 months dead (sepsis)
19	1998/Litofsky[67]	M/50	Brain	HIV	Surgery, no recurrence and metastasis, 8 months alive
20	1999/Blumenthal[68]	M/43	Brain	HIV	Chemotherapy, no recurrence and metastasis, 24 months alive
21	1999/Brown[69]	F/34	Brain	HIV	NA
22	1999/Tulbah[70]	M/6	Thyroid	Congenital T-cell immunodeficiency	No treatment, no recurrence and metastasis, 4 months lost follow-up

TABLE 2 (Continued)

No. of patients	Year/author/ref.	Age/sex	Site	Immune status	Treatment, recurrence, metastasis and outcome
23	2000/Rogatsch[71]	M/23	Multicentric tumor nodules in the liver, the paravertebral soft tissue, and in the muscle layer of a blood vessel at the ankle developed metachronously.	Cardiac transplantation, 2 years	Partial hepatectomy + under continuous antiviral therapy (famcyclovir), 18 months retroperitoneally with partial osteolytic destruction of the 11th rib and the other in the soft tissue near the processus transversus of the third thoracic vertebra altering the third rib, a painful subcutaneous nodule, 6 years recurrence, 9 years alive.
24	2000/Ritter[72]	F/5	Brain (left cavernous sinus)	HIV	NA
25	2000/Ritter[72]	F/35	Brain	HIV	NA
26	2001/Brichard[73]	F/6	Liver, multiple lesions	Liver transplantation, 1 year	Reduced immunosuppression + chemotherapy, no recurrence and metastasis 12 years alive with disease
27	2002/Reyes[25]	F/10	Larynx	Ataxia-telangiectasia	Surgery, no recurrence and metastasis, 9 months alive
28	2003/Ferri[74]	F/61	Thorax, bronus, multiple lesions	Kidney transplantation, 29 years	Surgery, no recurrence and metastasis, 2 years alive (disease-free)
29	2003/Tulvatana[75]	F/4	Iris	HIV	Inferior sector iridectomy (surgery), no recurrence and metastasis, died at 5 years and 6 months
30	2004/Zevallos-Giampietri[76]	M/29	Dura mater	HIV, 3 years	Subtotal resection + postoperatively radiotherapy, no recurrence and metastasis, 6 months after surgery lost follow-up
31	2005/Bonatti[77]	M/23	Liver, multiple lesions	Heart transplantation, 2 years	Surgery, reduced immunosuppression, mTOR inhibitor, antiviral drug, no recurrence and metastasis, 3 years alive (disease free)
32	2005/Suankratay[29]	F/4	Iris and abdominal wall	HIV, 4 years	Removal, no recurrence and metastasis, 12 months dead
33	2005/Suankratay[29]	F/43	Epidural of brain and spinal cord	HIV, 4 years	Removal + postoperative radiotherapy, no recurrence and metastasis, 4 months dead
34	2005/Suankratay[29]	M/32	Vocal cord	HIV, 4 years	Removal, no recurrence and metastasis, no metastasis and recurrence, 13 months alive
35	2006/Yokoi[78]	F/28	Lung	Immunocompetent	Surgery, pulmonary metastasis and recurrence, 12 months dead
36	2007/Chaves[79]	F/19	Brain, no multiple lesions	Lung transplantation, 1 year	Surgery, reduced immunosuppression, mTOR inhibitor, antiviral drug, no recurrence and metastasis, 4 months dead
37	2007/Nur[80]	M/24	Lung, liver, peritoneum, multiple lesions	Heart transplantation, 1 year	No treatment, dead (sepsis), diagnosed by autopsy
38	2007/Chan[81]	F/20	Abdominal wall	Systemic lupus erythematosus	Surgery, no metastasis and recurrence, 23 months alive
39	2010/Huang[39]	M/40	Vocal cord	Kidney transplantation, 14 years	Total laryngectomy, no metastasis and recurrence, 8 months dead

(Continues)

TABLE 2 (Continued)

No. of patients	Year/author/ref.	Age/sex	Site	Immune status	Treatment, recurrence, metastasis and outcome
40	2010/Gupta[82]	F/17	Intracranial mass	HIV, 14 years	Unresectable + the treatment plan included radiation therapy and single agent gemcitabine as a radiosensitizer. No metastasis and recurrence, 15 months alive
41	2010/Jeribi[83]	F/13	Liver, multiple lesions	Kidney transplantation, 3 years	Reduced immunosuppression, mTOR inhibitor, no metastasis and recurrence, 18 months alive with disease
42	2010/Sunde[84]	F/40	Uterus, no multiple lesions	Lung transplantation, 6 months	Surgery, reduced immunosuppression, antiviral drug, dead (sepsis)
43	2011/Suzuki[85]	F/8	Lung, multiple lesions	Kidney transplantation, 4 years	Surgery, reduced immunosuppression, antiviral drug, no metastasis and recurrence, 2 years alive (disease-free)
44	2011/Tetzlaff[86]	F/2	Left abdomen	HIV, 2 years	Complete excised, no metastasis and recurrence, 12 months alive
45	2011/Ramdial[87]	M/9	Thigh	HIV	Excision + total viral suppression, no metastasis and recurrence, 24 months alive
46	2011/Ramdial[87]	M/12	Leg	HIV	No treatment, no metastasis and recurrence, dead before further management
47	2011/Ramdial[87]	F/36	Orbit	HIV	Surgery (incomplete orbitectomy), no recurrence, brain metastasis, died of disease
48	2011/Ramdial[87]	F/29	Orbit	HIV	Surgery (incomplete orbitectomy), no metastasis and recurrence, died of pulmonary tuberculosis
49	2011/Ramdial[87]	M/28	Palate	HIV	NIL, no metastasis and recurrence, died of cryptococcal meningitis
50	2011/Sivendran[88]	M/43	Brain	HIV	Biopsy and resection + anti-retroviral therapy, no metastasis and recurrence, 20 months alive
51	2013/Takei[89]	M/27	Brain	Hodgkin lymphoma	Surgery, no metastasis and recurrence, 2 years alive
52	2013/Chelimilla[90]	M/54	Liver	HIV	NA
53	2014/Jericho[91]	F/2	Liver, multiple lesions	Liver transplantation, 15 months	Surgery, reduced immunosuppression, 7 months recurrence, no metastasis, 31 months alive
54	2015/Hamed[92]	F/71	Liver	Kidney transplantation	Surgery, no metastasis and recurrence, 40 months alive
55	2016/Agarwal[93]	F/40	Spinal canal from T2-5	HIV	Resection, no metastasis and recurrence, 4 years alive
56	2016/Agarwal[93]	F/12	T4 spine	HIV	Surgery under microscope microneurosurgical technique with cauterization, liver metastasis 1 month later + chemotherapy, no recurrence, 8 years alive

TABLE 2 (Continued)

No. of patients	Year/author/ref.	Age/sex	Site	Immune status	Treatment, recurrence, metastasis and outcome
57	2017/Munjal[94]	F/34	Dorsolumbar spine	HIV	Near-total excision of the tumor + antiretroviral combination drug therapy, no metastasis and recurrence, 1 month alive
58	2019/Aida[95]	F/30	Liver, lung	Kidney transplantation from a living relation (the donor was her mother) 4 years ago	Left lateral segmentectomy + chemotherapy, no metastasis and recurrence, 7 months dead
59	2020/Morales[96]	M/23	Brain	HIV	Radiotherapy, no metastasis and recurrence, 6 months alive
60	2020/Reddy[97]	M34	Left arm	HIV	Surgery, no metastasis and recurrence, 16 months alive
61	2022/Li[99]	M/7	Multiple hypermetabolic lesions in the liver, lung, and lymph nodes.	Wiskott-Aldrich syndrome	NA
62	Present case	M/20	Vocal cord	HIV	CO_2 laser surgery, no metastasis and recurrence, 3 months alive

Abbreviation: NA, not available.

10-year-old girl with a history of ataxia telangiectasia (AT) 5 years prior, who underwent right partial supraglottic laryngectomy due to LLMS. Approximately 8 months later, a jejunal mass was detected and subsequently confirmed to be leiomyoma. EBV ISH was strongly positive.[25] Therefore, AT may be a risk factor for LMS. AT is a chromosome breakage syndrome, together with Bloom's syndrome, Fanconi's anemia, xeroderma pigmentosa, and Nijmegen breakage syndrome. Chromosomal breakage syndromes are characterized by chromosome instability as a result of autosomal recessive defects of DNA repair mechanisms.[113,114] They are a risk factor for lymphoma, leukemia, various cancers, and osteosarcoma.[113]

Patients with Sézary syndrome (SS) are predisposed to secondary malignancies.[115,116] SS is a leukemic form of epidermotropic cutaneous T-cell lymphoma characterized by pruritus and squamous erythroderma. Among patients with SS, 27% develop a secondary malignancy.[17] Ingen-Housz-Oro et al.[23] reported a 78-year-old female patient with LLMS who had a history of SS; she was negative for EBV by immunochemistry and ISH. The carcinogenic side effect of chlorambucil used for SS might increase the risk for a secondary LMS.[23]

Liver LMS may be associated with a history of cirrhosis.[117,118] Delis et al.[119] reported a patient with LMS of the inferior vena cava who had a history of cirrhosis. Preti et al.[26] reported a patient with LMS who had a history of cirrhosis.

EBV is associated with lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, gastric adenocarcinoma, and lymphoepithelioma-like carcinomas.[119–122] EBV associated with smooth muscle tumor (SMT) of the larynx has been reported.[123] Whaley et al.[123] identified 12 cases of EBV-associated laryngeal SMT. To the best of our knowledge, only four cases of EBV-associated LLMS have been reported,[25,29,39] including the present case.

3.2 | EBV-associated LLMS and LMS

EBV-associated LMS may be multifocal/multicentric disease, including LLMS.[29] Some EBV-associated SMTs lack important characteristics of LMS, that is, severe nuclear atypia, epithelioid features, atypical mitoses, tumor necrosis, and destructive invasion.[123,124] Thus, SMT is not LMS. We searched PubMed for English-language articles using the keywords "Epstein-Barr virus associated leiomyosarcoma" or "EBV and leiomyosarcoma" or "EBV and smooth muscle tumor" or "Epstein-Barr virus associated smooth muscle tumor;" SMTs were excluded. Our patient presented with disease in the larynx but no other sites during the follow-up period, as reported previously.[39] However, the follow-up was of insufficient duration.

TABLE 3 Summary of clinical features of 62 patients with EBV-associated leiomyosarcoma

Clinical features	No. of patients (%)
Sex	
Female	35 (56.5)
Male	27 (43.5)
Age	
<10 years old	18 (29.1)
10–20 years old	10 (16.1)
>20 years old	34 (54.8)
Past medical history	
HIV infection	36 (58.1)
Post-transplantation	18 (29.1)
Acute lymphoblastic leukemia	1 (1.6)
Common variable immunodeficiency syndrome	1 (1.6)
Congenital T-cell immunodeficiency	1 (1.6)
Systemic lupus erythematosus	1 (1.6)
Ataxia-telangiectasia	1 (1.6)
Wiskott-Aldrich syndrome	1 (1.6)
Hodgkin's lymphoma	1 (1.6)
Immunocompetent	1 (1.6)
Location	
Central nervous system	17 (27.4)
Gastrointestinal tract	6 (9.7)
Larynx	4 (6.5)
Liver	4 (6.5)
Extremities	3 (4.8)
Eye	3 (4.8)
Adrenal gland	2 (3.2)
Lung	2 (3.2)
Kidney	1 (1.6)
Thyroid gland	1 (1.6)
Palate	1 (1.6)
Multiple lesions	18 (29.1)

TABLE 4 Clinicopathologic features and survival of 53 laryngeal leiomyosarcoma patients with complete follow-up data

Clinicopathologic factors	No. of patients (%)
Sex	
Female	5 (9.4)
Male	48 (90.6)
Age	
<60	17 (32.1)
≥60	36 (67.9)
Symptom	
Hoarseness	20 (37.7)
Dysphonia	6 (11.3)
Dyspnea	2 (3.8)
Stridor	1 (1.9)
Difficulty swallowing	1 (1.9)
Dysphagia	1 (1.9)
Respiratory distress	2 (3.8)
Overlapping presentations	20 (37.7)
Site	
Glottis	35 (66.1)
Supraglottis	12 (22.6)
Subglottis	5 (9.4)
Transglottis	1 (1.9)
EBV-associated	
Yes	4 (7.5)
No	49 (92.5)
Treatment	
Surgery	36 (67.9)
Radiotherapy	1 (1.9)
Surgery + postoperative RT	16 (30.2)
Recurrence	
Yes	9 (17.0)
No	44 (83.0)
Distant metastasis	
Yes	10 (18.9)
No	43 (81.1)
Neck lymph node metastasis	
Yes	1 (1.9)
No	52 (98.1)
Death	
Yes	8 (15.1)
No	45 (84.9)

The role of EBV in the pathogenesis of LMS is unclear. EBV-associated LMS, previously associated with transplantation, is now common in HIV-infected patients, particularly children. We found only 62 cases of EBV-associated LMS, including the present case. Information about the clinical features is given in Table 2 and summarized in Table 3. Of the 62 patients, 61 (98.4%) were immunosuppressed and 1 (1.6%) was immunocompetent, albeit with a 4-year history of EBV infection.[78] The integration of EBV into smooth muscle cells may be important in the development of LMS in the immunocompetent.[78] In the immunosuppressed, EBV may enter smooth muscle cells via CD21 as a receptor.[59,86,122]

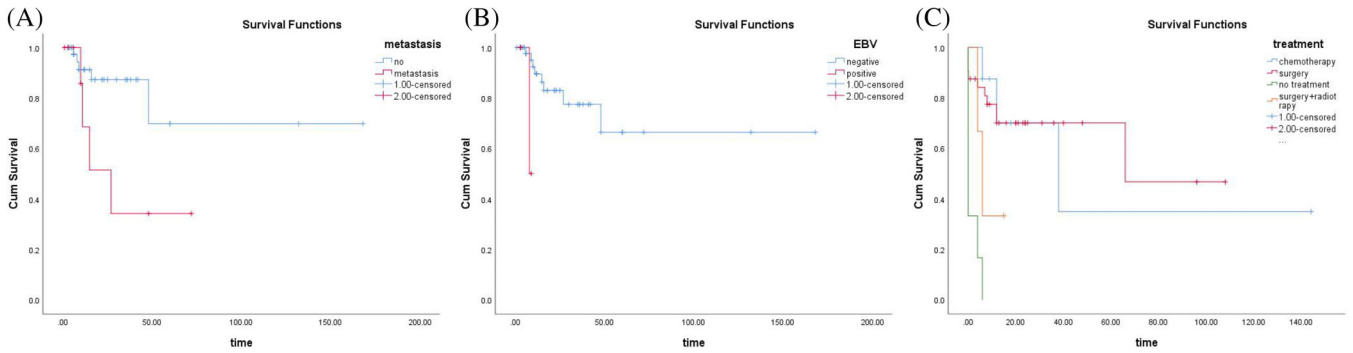

FIGURE 4 Prognostic factors of LLMS or EBV-associated LMS. A: Distant metastasis was associated with poor survival ($p = 0.040$). B: Log-rank analysis showed that EBV infection was associated with a decreased survival rate among patients with LLMS ($p = 0.01$). C: Log-rank analysis showed that the survival rate of EBV-associated LMS was increased by treatment ($p < 0.0001$) other than postoperative RT. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/LN4Axu. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 shows that there were multiple EBV-associated LMS in 18 cases (29.5%). Such multifocal lesions are multiple, independent primary lesions rather than metastases.[122,125]

3.3 | Outcomes and treatment

Of 61 patients with LLMS, 53 had complete follow-up data, summarized in Table 4. None of the patients presented with nodal or distant metastases at the time of diagnosis. One patient had neck lymph node metastasis 10 months after total laryngectomy.[10] In addition, 10 patients (18.9%) had distant metastases to the lung (6, 60.0%),[13,14,26,33,47,52] left axillary nodes (1, 10.0%),[42] liver and lung (1, 10.0%),[53] thyroid gland and lung (1, 10.0%),[19] and multiple metastases (1, 10.0%; neck, lung, bone marrow, liver, adrenal glands, colon, spleen, heart, and thyroid gland).[5] The LMS cases with distant metastases were in the glottis (five cases), supraglottis (two cases), subglottis (two cases), and transglottis (one case). There were no significant differences between the distant metastasis and no distant metastasis (Fisher's exact test, $p = 0.467$). Nine patients (17.0%) had local recurrence (1–16 months after primary surgery).[1,4,5,23,30,46,52,58,59] These patients underwent a second resection. The cases of recurrent LMS were in the glottis (four cases), supraglottis (two cases), subglottis (two cases), and transglottis (one case). Eight patients died of disease (15.1%) after a median of 11.2 months (range 8–16 months).[1,5,19,23,25,33,39,53]

Among 53 patients, 20 (37.7%) underwent total laryngectomy (TL), 8 (15.1%) underwent laryngectomy via CO2 laser under microlaryngoscopy, 15 (28.3%) underwent surgery and postoperative radiotherapy (RT) (7 patients, TL plus RT; 5 patients, partial laryngectomy plus RT; 3 patients, CO_2 laser plus RT), 6 patients (9.8%) underwent partial laryngectomy, and 1 patient (1.9%) received only RT. One patient (1.9%) received chemotherapy and neoadjuvant RT (60 Gy) due to invasion of the prevertebral space and encasement of the left internal and external carotid arteries, followed by pharyngolaryngo-esophagectomy, total thyroidectomy, and bilateral-modified radical neck dissection with formation of a neoesophagus from an interpositional jejunal free-flap. However, he developed liver and lung metastases, received palliative chemotherapy, and died of his disease 10 months later.[53] Eight patients (15.1%) received neck dissection; however, no cervical lymph-node metastasis was observed. Neck lymph node recurrence was no statistically different between the patients who received neck dissection and patients who did not (Fisher's exact test, $p = 1.000$). Therefore, neck dissection is unnecessary for LLMS unless there is pathologic lymphadenopathy, because the primary route of metastasis is hematogenous.

The overall 5-year survival rate was 64.0%. The survival rate did not differ significantly according to sex ($p = 0.395$), age ($p = 0.391$), site ($p = 0.213$), treatment modality ($p = 0.232$), or recurrence ($p = 0.161$). Distant metastases affected the overall survival of patients with LLMS ($p = 0.040$, Figure 4A). Interestingly, EBV infection was a prognostic factor: EBV-positive patients had a poor survival rate ($p = 0.01$, Figure 4B).

Among 62 patients with EBV-associated LMS, 49 had complete follow-up data (Table 2). Four patients (8.2%) had distant metastases: to the lungs (one case[78]), brain (one case[87]), liver (one case[93]), and multiple metastases (one case; rib, soft tissue near the processus transversus of the third thoracic vertebra, and a subcutaneous nodule[71]). Four patients (8.2%) had local recurrence (7 months to 6 years after primary surgery).[71,79,88,91] Eighteen patients died of their disease (36.7%)[29,39,58,60,62,65,66,75,78–80,84,87,95]; three of those were diagnosed at autopsy.[60,66,80] The overall 5-year

survival rate was 50.0%. The survival rate did not significantly differ according to sex, age, single or multiple lesions, distant metastasis, and recurrence. Treatment modalities affected the overall survival of EBV-associated LMS ($p < 0.0001$, Figure 4C). The survival rate was higher among patients who received treatment than among those who did not. However, postoperative RT did not improve the survival rate. The survival rate did not differ significantly between EBV-associated LMS and that at other sites ($p = 0.686$).

4 | CONCLUSIONS

EBV-associated LLMS is rare; only four cases have been reported. EBV infection may be a poor prognostic factor for LLMS.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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