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ORIGINAL PAPER

Epstein-Barr Virus-Associated Smooth Muscle Tumors of Larynx: A Clinicopathologic Study and Comprehensive Literature Review of 12 Cases

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Abstract
Laryngeal mesenchymal neoplasms are rare, with smooth muscle tumors comprising a small subset. Specifically, Epstein-Barr virus (EBV)-associated smooth muscle tumors are exceptionally rare, lacking a comprehensive evaluation of their clinical and histologic features. Two patients (a 59 year old male and 51 year old female) had received renal transplants 156 and 240 months, respectively prior to onset of laryngeal symptoms. Supraglottic polypoid masses were identified and removed conservatively. Histologically, the tumors were hypercellular, showing alternating light and dark areas, the latter composed of primitive appearing round cells, while a more characteristic spindled tumor cell population was noted in the remaining areas. Cytoplasmic vacuoles were noted adjacent to the nucleus. There was no tumor necrosis or pleomorphism, but increased mitotic figures (11–12/2 mm^2) were seen, without atypical forms. The tumor cells were strongly immunoreactive with smooth muscle actin and smooth muscle myosin heavy chain and with Epstein-Barr virus encoded RNA (EBER) by in situ hybridization. These patients were reviewed in the context of a thorough English literature review, which demonstrates a wide age range at presentation without a sex predilection, but with most patients from specific ethnic groups (Chinese, Thai, Pilipino). Three-quarters of patients are part of multifocal disease and the majority are post-renal transplantation patients. Conservative management seems to yield the best overall outcome for these indolent tumors. In conclusion, EBV-associated smooth muscle tumors should be considered in any immunocompromised patient with a head and neck smooth muscle tumor, especially when EBER is documented by in situ hybridization. Conservative management may be employed, even when multifocal tumors are documented.

Keywords Laryngeal neoplasms · Smooth muscle tumor · EBV-association · Kidney transplantation · Immunocompromised host

Introduction

Within the head and neck, cutaneous and soft tissue site leiomyosarcomas are the most common, including metastases to skin [1–3]. However, mucosal site leiomyosarcomas are rare, identified in decreasing order of frequency in the sinonasal tract, oral cavity, and larynx, with single case reports of other head and neck sites [4–13]. Therefore, primary smooth muscle tumors of the larynx are very rare. Epstein-Barr virus (EBV)-associated smooth muscle tumors are exceptionally rare in the head and neck region [14–18], and tend to be identified in immunocompromised patients, usually secondary to immunosuppressive therapy (post-transplant), human immunodeficiency virus (HIV) infection, or severe malnutrition [14, 19, 20]. By definition, EBV-associated smooth muscle tumors are smooth muscle tumors that have EBV-association, mostly identified in immunosuppressed patients, and commonly associated with multicentricity [14, 17]. The rarity of the tumor contributes to a lack of good understanding about diagnosis, management, and outcome. This study reports two additional patients with EBV-associated smooth

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muscle tumors of the larynx, and presents the findings in the context of a thorough English literature review.

Materials and Methods

This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of an Internal Review Board authorization (#5968) performed under the direction of Southern California Permanente Medical Group relating to human subjects in research.

Immunophenotypic analysis was performed in both cases on a single block from each case by a standardized Envision™ method employing 4 μm-thick, formalin fixed, paraffin embedded sections. Epitope retrieval was performed, as required by the manufacturer guidelines. In situ hybridization was performed for EBER by standard techniques. Standard positive and negative controls were used throughout.

A review of the English literature was based on a PubMed search from 1966 to 2021 with all cases of laryngeal smooth muscle tumors reviewed (approximately 70 cases), and then focused on EBV-associated tumors specifically. Cases were excluded if they did not include clinical information, imaging findings, pathology descriptions and/or images, and lacked clinical follow-up data. Specific attention was given to clinical series which included immunohistochemistry information. Potential duplicate reporting was evaluated (8 potential cases were reported from Singapore), with the reports with the most clinical information utilized [14–16, 21, 22].

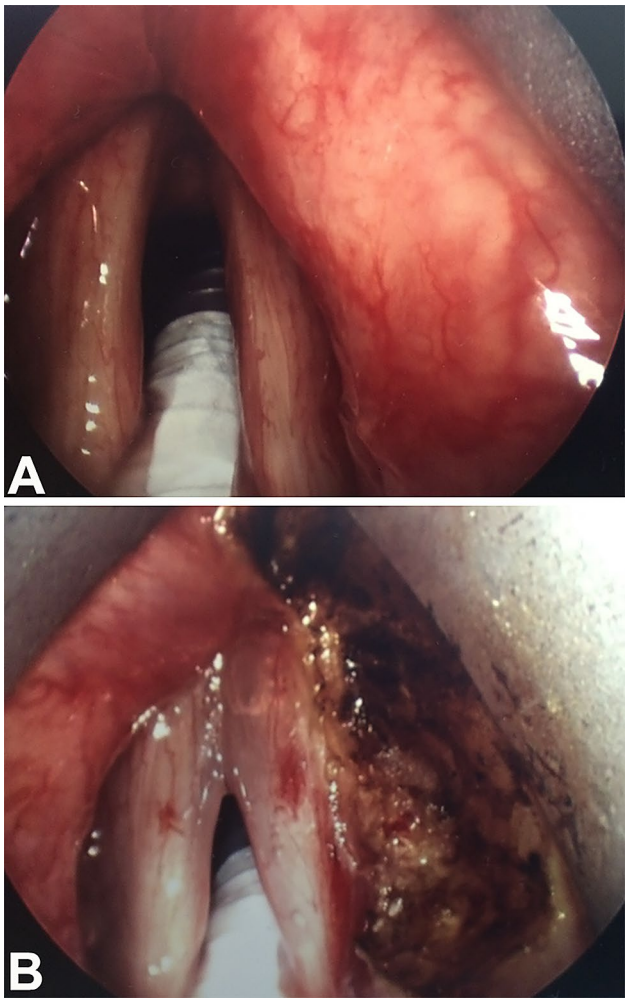

Fig. 1 **a** Laryngoscopy demonstrating a mass over the right false vocal fold (case #1). **b** Postoperative view of the same area, demonstrating complete resection of the mass

Clinical Cases

Case 1

A 59-year-old Pilipino presented to the otorhinolaryngology service with an ongoing history of chronic hoarseness, cough and upper respiratory tract infection, for the past 2 months. There was mild right-sided chest pain with swallowing solids. There was no otalgia, neck masses, unintended weight loss, hemoptysis, or dyspnea. The patient was a former cigarette smoker (20 pack-year history, quit 13 years prior to visit). He reported no fevers, chills or night sweating. There was no family or personal history of cancers. Physical exam documented a breathy vocal quality. Fiberoptic nasopharyngolaryngoscopy identified an erythematous, smooth, pedunculated, round, right mid-false cord mass (Fig. 1). Initial stroboscopy identified a well circumscribed right vocal fold mass impairing symmetric mucosal wave. The patient had a history of renal transplant (13 years earlier from a living unrelated donor) after developing end-stage renal disease secondary to hypertensive nephrosclerosis; he had been on arteriovenous graft hemodialysis for 5 years. He was maintained on combination cyclosporine and prednisone without rejection symptoms. His course was complicated by pyelonephritis and a kidney abscess, managed medically and through drainage. The patient's past medical history includes prediabetes and gout, both medically managed.

A transoral biopsy of the right glottic lesion was performed via indirect laryngoscopy. Follow-up computed tomography did not show any residual mass lesion, although there was soft tissue asymmetry at the level of the false vocal fold. As such, an endoscopic partial laryngectomy was performed, with laser resection around the false cord. He recovered uneventfully, and is free of local recurrence or metastatic disease, 67 months after initial presentation.

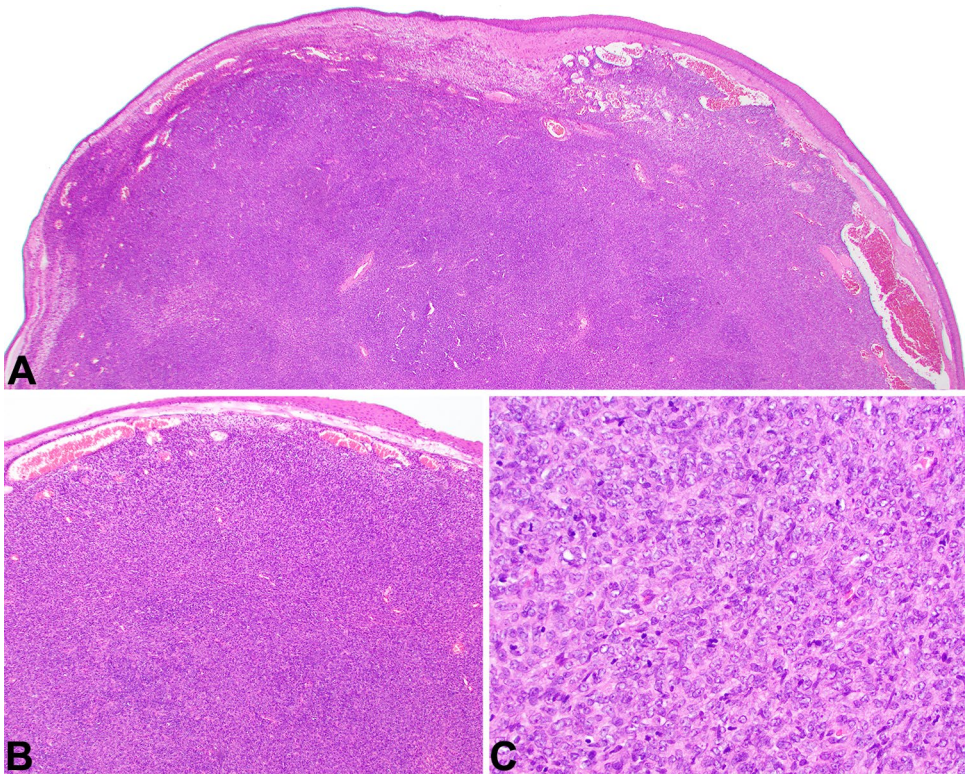

Fig. 2 **a** An intact squamous epithelium is noted above the neoplastic proliferation. There is a vague checkerboard light and dark appearance. **b** The neoplasm shows epithelioid spindled cells below the surface epithelium. **c** The tumor is highly cellular, showing vesicular, open nuclear chromatin of box-shaped to oval nuclei

The gross specimen was a polypoid 1.0 × 1.0 × 0.7 cm hemorrhagic, firm to pale soft tissue fragment. Histologically, there was an intact squamous epithelium. There was a grenz zone of separation between the surface epithelium and the neoplastic proliferation (Fig. 2a). The stroma was entirely filled by a very cellular tumor, present at the stalk of the sample. A marbleized appearance at low power showed light and dark areas of an alternating or checkerboard appearance (Fig. 2a). The cells were arranged in a solid to more fascicular appearance. The neoplastic cells demonstrated a very high nuclear to cytoplasmic ratio with a vaguely syncytial quality (Fig. 2b). The nuclei were irregular with vesicular to open nuclear chromatin and easily identified nucleoli (Fig. 2c). A rounded or more primitive appearance was seen in some areas, which then blended with more spindled areas. Small vessels are noted throughout. There was no keloid-like collagen, no wiry collagen, and no mucoid or myxoid substance in the background. There was an increased mitotic rate, with 11 mitotic figures/2 mm^2 (Fig. 3a), including atypical forms (Ki-67 labelling index of 39%; 75 of 192 cells counted in a single high power hot spot field). Isolated inflammatory cells were seen within the proliferation.

By immunohistochemistry, the neoplastic cells were strongly and diffusely immunoreactive with smooth muscle actin (Fig. 3b), muscle specific actin, and smooth muscle myosin heavy chain (Fig. 3c), while negative with pancytokeratin (AE1/AE3), EMA, ß-catenin, CD34, S100 protein, SOX10, HMB45, Melan-A, ALK-1, TLE1 and claudin-1. The EBER in situ hybridization demonstrated a strong, diffuse, nuclear result throughout the tumor (Fig. 3d).

The follow-up resection did not have any residual tumor, with surgery site changes only.

Case 2

A 51-year-old Pilipina presented to the otorhinolaryngology service with a 3 month history of chronic rhinosinusitis and throat pain. The patient experienced difficulty when swallowing, especially pronounced on the right side. Endoscopic exam demonstrated an inflamed cyst-like lesion on the right arytenoid (Fig. 4). The patient was a never smoker.

The patient had a history of renal transplant (20 years earlier from a living related [sibling] donor) after developing end stage renal disease secondary to IgA nephropathy diagnosed at age 28, with initial hemodialysis followed by peritoneal dialysis for 2 years. After a bout of subacute rejection, her condition stabilized. She was maintained on prednisone, tacrolimus, and mycophenolate sodium. The allograft failed after 5 years, and was removed due to pain. After peritoneal dialysis for 2 years, she underwent cadaveric renal transplant, which required several units of whole blood transfusions. Early acute rejection was managed with thymoglobin. She experienced episodes of acute rejection, with changes in immunosuppressive therapy to manage her rejection. Her medical history included hypertension for

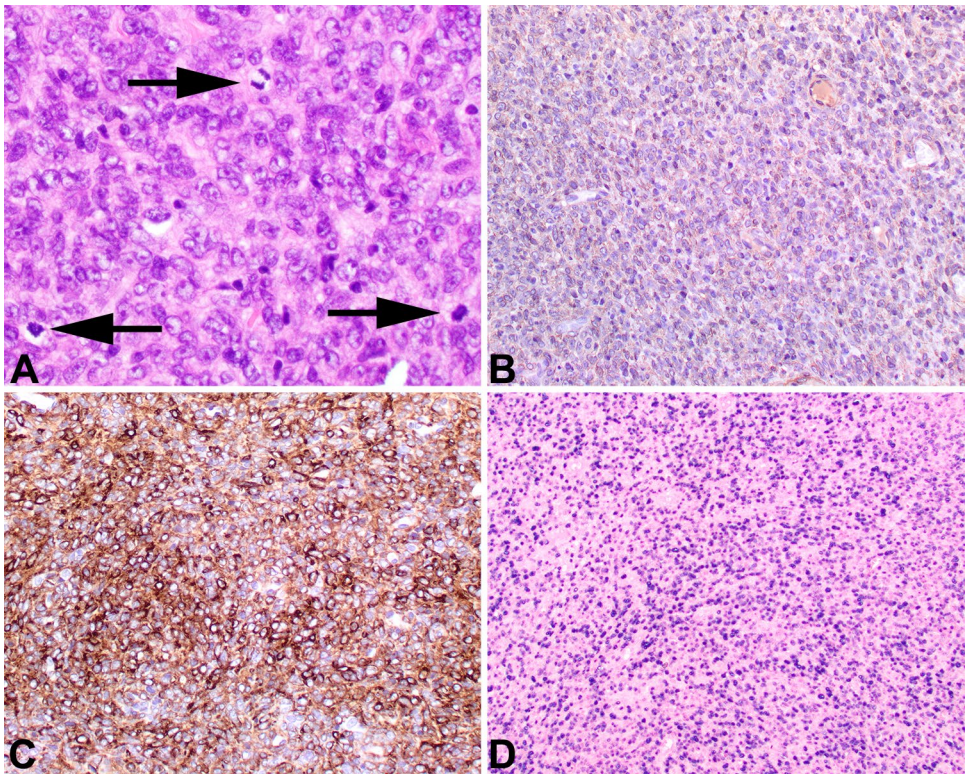

Fig. 3 **a** Numerous mitoses were easily identified, with a single high power field demonstrating 3 mitotic figures (black arrows). **b** The neoplastic cells show a diffuse reaction with smooth muscle actin, and **c** with smooth muscle myosin heavy chain. **d** There is a strong nuclear reaction with EBER by in situ hybridization

22 years (treated with metoprolol tartrate), and secondary hyperparathyroidism, hyperthyroidism, gastroesophageal reflux disease, and migraines. Other than the transplants, her surgical history included a hysterectomy for leiomyomata. Her family history was significant for her father's cousin reported to also have IgA nephropathy and he had undergone two cadaveric renal transplantations.

Following surgery, which removed the bed of the arytenoid and used CO_2 laser ablation, no residual tumor was identified histologically. Radiation was given shortly after surgery with opposed lateral beams over a 6 week period to a total dose of 60 Gy. There has been no documented recurrent disease or metastatic disease, 12 months after initial presentation.

The initial gross specimen was a $0.8 \times 0.8 \times 0.7$ cm irregular, tan-pink fragment of tissue that was entirely submitted.

Histologically, the surface squamous epithelium was most intact, with focal areas of erosion, but with a grenz zone of separation between the surface and the soft tissue tumor. The neoplasm was cellular with tumor noted at all of the sample borders (Fig. 5a). The cells were arranged in a solid to storiform-fascicular architecture (Fig. 5b), with numerous vessels noted at the periphery. The neoplastic cells were seen scrolling off the vessels wall, suggesting a point of origin. The neoplastic cells had a very high nuclear to cytoplasmic ratio, with a vaguely syncytial quality. A primitive and rounded cellular appearance was seen in the majority of the tumor, but other areas showed a more spindled appearance. The nuclei were irregular with vesicular to open nuclear chromatin, and prominent nucleoli (Fig. 5c). Perinuclear vacuoles were seen compressing the nuclei which had a box-shape (Fig. 5d). Mitotic figures were easily identified with 12 mitotic figures/2 mm^2, including atypical forms (Ki-67 labelling index of 18.5%; 50 of 271 cells counted in a single high power hot spot field; Fig. 6a).

By immunohistochemistry, the neoplastic cells showed a strong and diffuse cytoplasmic reaction with smooth muscle actin (Fig. 6b) and smooth muscle myosin heavy chain (Fig. 6c), while showing a strong nuclear reaction with p53 and a diffuse nuclear reaction with EBER (by in situ hybridization; Fig. 6d). The neoplastic cells were negative for pancytokeratin (AE1/AE3), p63, myogenin, S100 protein, HMB45, SOX10, EMA, TLE1, and CD99.

There was no residual tumor in the resection margin samples of the re-excision specimen.

Discussion

Mesenchymal tumors of the larynx are uncommon, with most accounted for by chondrosarcoma [23–28]. However, there are case reports of inflammatory myofibroblastic tumor [29–31], schwannoma, solitary fibrous tumor [32], synovial sarcoma [25], leiomyosarcoma, and rhabdomyosarcoma [33]. The smooth muscle tumor category is therefore quite

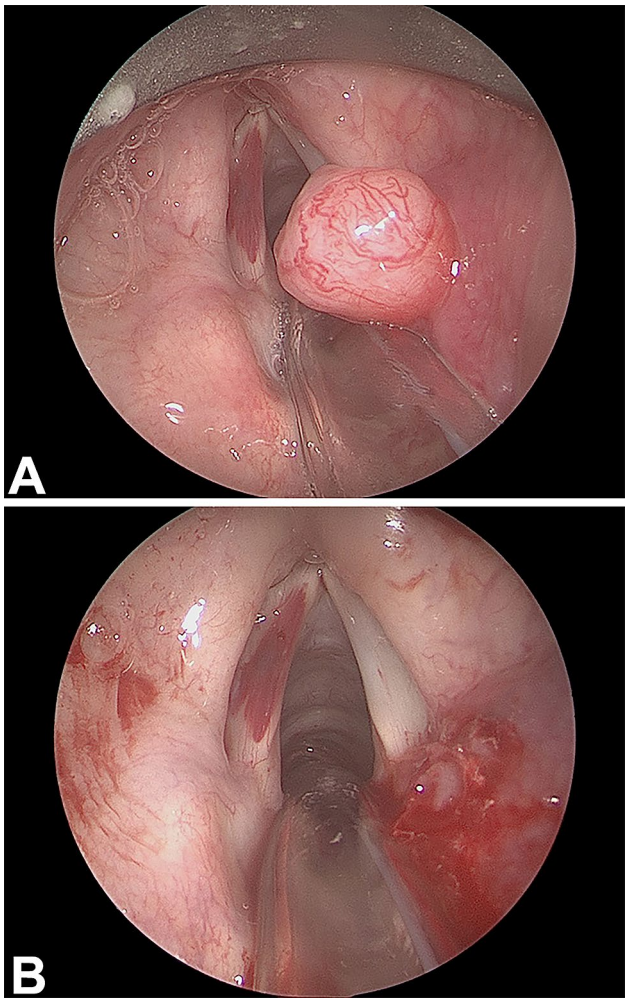

Fig. 4 **a** Laryngoscopy demonstrating a polypoid mass (case #2). **b** Postoperative view of the same area, demonstrating resection of the mass

rare, with leiomyosarcomas much more commonly identified than leiomyomas [34–36]. In general, leiomyosarcomas account for < 0.2% of all laryngeal malignancies [27]. However, the category of EBV-associated smooth muscle tumors is an intermediate category of tumors with very few cases reported (Table 1) [14–18, 21, 22, 37].

Based on the 10 reported literature cases and the two current cases, there is a broad age range at presentation, from 8 to 59 years, with a median of 42.5 years and an average of 38.5 years. Females show a median age of 49 years and an average of 36.4 years, while males have a median age of 32 years and an average of 41.4 years. It is noteworthy that the majority of patients are of Asian ethnicity (Chinese = 4; Thai = 3; Pilipino = 2), with two Latinas. While it cannot be definitively documented, race or ethnicity may be a co-factor in the development of this EBV-associated tumor, perhaps similar to the very strong association with EBV-driven nasopharyngeal carcinoma in similar ethnic cohorts (southeast Asians). The patients with a primary immunodeficiency due to genetic or environmental causes (malnutrition) were both female children (8 and 9 years, respectively), while the transplantation patients were a median of 50.5 years (average, 45.5 years), and the HIV-associated patients were a median of 40.5 years (average 40.5 years). There is a defined period from the transplantation or HIV-diagnosis to the development of the tumor, with a median of 48 months (average, 92.6 months), suggesting a latency period before tumor development. There is an equal sex distribution, although both of the primary immunodeficiency-associated patients were female [18, 37]. In the post-transplantation setting, all of the cases reported are in renal transplant patients. Viewed differently, in a large cohort of renal transplantation patients, 8 EBV-associated smooth muscle tumors were identified in 1123 transplant patients, yielding a 0.7% incidence in transplant patients [16]. The etiology involves EBV infection in the setting of T-lymphocyte immunosuppression, with pathogenesis postulated to involve specifically the EBV type III latency pattern, with mTOR pathway activation [16, 38]. Further, the degree of immunosuppression induced may increase the likelihood of tumor development rather than age alone.

Symptoms are non-specific, but dysphonia, hoarseness, dyspnea, and cough along with pain, are all noted. The tumor involves the glottis (true vocal cords, n = 6), supraglottis (n = 4) or subglottic zone (n = 3), including one tumor showing a transglottic presentation. Macroscopically, laryngeal tumors are much smaller than other anatomic sites, with all described tumors 2.5 cm or less, with a median of 1.8 cm (mean, 1.7 cm), probably due to the anatomic confines of the region resulting in symptomatic presentation due to airway obstruction. Tumors show a grey-white cut surface.

It is always challenging to tell multifocal tumors versus metastatic tumors, but in 8 of the 12 reported cases, multifocal tumors are seen [14–17, 22, 37], with the possibility of multifocal tumors in one of the patients who had a gastric resection for an unknown tumor type [18]. Tumors involved the liver, lung, dura-epidural space, spleen, kidney, soft tissues, jejunum, adrenal gland, nasopharynx, tonsils, and spine, along with the larynx. However, given the usual lack of pleomorphism, lack of tumor necrosis, and lack of local recurrence, it would seem that multifocal tumor is more likely than metastatic disease.

The histologic findings of these smooth muscle tumors is the much more primitive appearance to the tumor cells, whether seen as hypercellular nodules or the dominant finding in the tumor. Whereas intersecting fascicles of spindled cells with eosinophilic cytoplasm and elongated blunt-ended nuclei are sometimes seen, along with box-shaped nuclei with perinuclear vacuoles, the short, blunt cells have a more rounded appearance, a high nuclear to cytoplasmic ratio, nuclear chromatin clearing, and a more solid

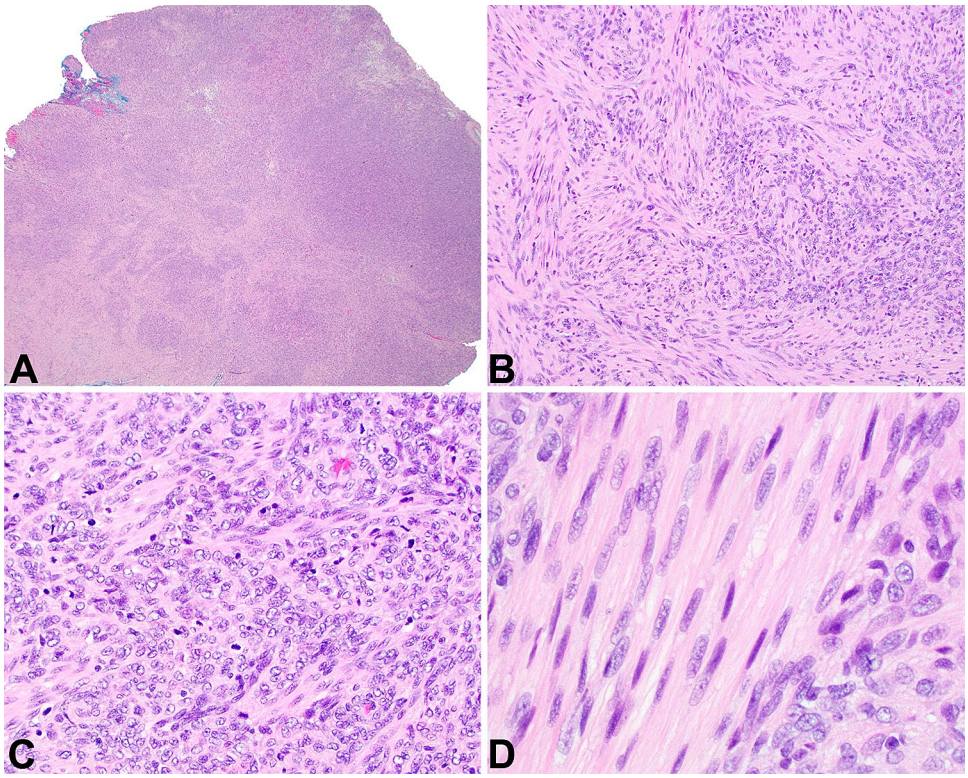

Fig. 5 **a** A cellular tumor is noted on the borders of the biopsy. There are alternating light and dark areas, corresponding to hypo- and hypercellular regions, respectively. **b** Short interlacing fascicles of spindled neoplastic cells. **c** The primitive neoplastic cells have an increased nuclear to cytoplasmic ratio. **d** Perinuclear vacuoles are identified adjacent to and partly compressing the box-shaped nuclei

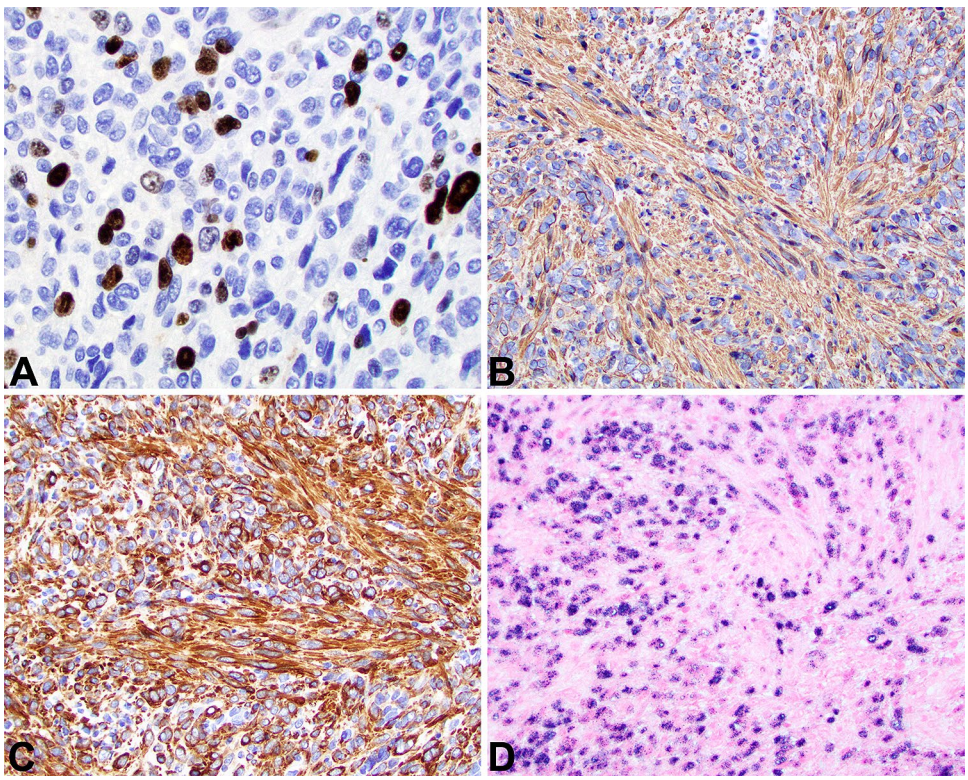

Fig. 6 **a** The Ki-67 labelling index showed numerous positive nuclei. **b** The neoplastic cells are strongly immunoreactive with smooth muscle actin, **c** smooth muscle myosin heavy chain, and **d** nuclear EBER by in situ hybridization

growth. Importantly, there is limited pleomorphism, with a monotonous overall appearance [14, 17]. When seen, these features may broaden the differential diagnosis. Vascular association may be seen [39, 40], appearing to be the source of the tumor in some cases. An inflammatory infiltrate may be seen sprinkled throughout, but is not to the same degree

Table 1 Patient Information for Laryngeal EBV-associated Smooth Muscle Tumors (Literature Review and Current Cases)

Case No.	Age (years); sex; race	Symptoms; duration in months; site	Immunosuppression	Time to tumor development (mo.) from date of initial immunocompromise	Size (cm)	Mitotic rate /10 HFPs	Treatment	Multifocal disease; sites	Recurrence	Status; follow-up duration (mo.)
1 (Reyes) [37]	9; F; Latina	Dyspnea; rapid onset; supraglottic	Ataxia telangiectasia	60	2.5	7	Partial supraglottic laryngectomy	Yes; jejunum	No	Alive, NED; 8
2 (Deyrup) [14]	50; F	Glottic	Renal transplant	30	n/r	11	Excision	Yes; lung, extradural	No	Dead, NED; 105
3 (Deyrup) [14]	31; M; Thai	Subglottic	Renal transplant	39	n/r	3	Excision	Yes; tonsil, nasopharynx	No	Alive, with disease; 2
4 (Suankratay) [15]*	49; F; Thai	Dysphonia; 1; glottic	HIV	48	n/r	3	Excision	Yes; epidural, orbit, adrenal glands	No	Dead, with disease; 48
5 (Suankratay) [15]*	32; M; Thai	Hoarseness; 6; glottic	HIV	48	n/r	11	Excision	No	No	Alive, NED; 84
6 (Gan) [22]	36; F; Chinese	Throat discomfort; 12; glottic	Renal transplant	158	1.5	n/r	Excision	No	No	Alive, NED; 5
7 (Ong) [16]	31; M; Chinese	Glottic	Renal transplant	48	n/r	n/r	None	Yes; pharynx, lungs, adrenal, liver, spleen, kidney	No	Alive, with disease; 60
8 (Ong) [16]	52; F; Chinese	Glottic	Renal transplant	24	n/r	n/r	Partial resection	Yes; lung, liver, spine	No	Dead, with disease; 108
9 (Huang) [17]	54; M; Chinese	Progressive stridor; subglottic	Renal transplant	168	2.0	3	Laryngectomy	Yes; leg soft tissue	No	Alive, NED; 8
10 (Soares) [18]	8; F; Guatemalan	Incidental; transglottic	Undernourished	n/a	2.4	Low	Excision	Maybe; gastric resection for unknown reason	No	Alive, NED; 12
11 (Current)	59; M; Pilipino	Chronic hoarseness, cough; 2; supraglottic	Renal transplant	156	1.0	11	Excision	No	No	Alive, NED; 67
12 (Current)	51; F; Pilipina	Throat pain, difficulty swallowing, rhinosinusitis; 3; supraglottic	Renal transplant	240	0.8	12	Excision	No	No	Alive, NED; 12

F, female; *M*, male; *mo*., months; cm, centimeters; *HPF*, high power fields; *NED*, no evidence of disease; *n/r*, not reported

*These 2 patients were included in a later report by Issarachaikul, et al. [21]

as seen in inflammatory myofibroblastic tumor. Necrosis is not described in the tumors. The mitotic index is increased, with a median in the reported cases of 9 mitotic figures/10 high power fields, or 12 mitotic figures/2 mm^2 for the current two reported cases. This relatively high mitotic index is usually a finding of leiomyosarcoma, although leiomyomas with increased mitoses are certainly recognized, and are a well-accepted phenomenon in other organs, such as the uterus [41, 42]. Leiomyosarcomas show moderate to severe nuclear atypia, epithelioid features, atypical mitoses, tumor necrosis, and destructive invasion. As these features are not identified in these EBV-associated neoplasms, the classification as *EBV-associated smooth muscle tumor* more accurately reflects the biologic behavior (i.e., tumor rather than sarcoma).

By immunohistochemistry, the neoplastic cells show diffuse reactions with SMA and h-caldesmon, while muscle specific actin, smooth muscle myosin heavy chain, and desmin expression is more variable [6, 7, 10, 14–18, 22, 43]. Reactivity with EBER by in situ hybridization is a consistent finding, recognizing that EBV-latent membrane protein or even CD21 (the receptor for EBV) may not be positive, and in fact are usually reported to be negative [14, 16, 17, 22].

Given the laryngeal anatomic site, a selection of benign and malignant spindle-cell to round cell neoplasms are considered, including peripheral nerve sheath tumors, solitary fibrous tumor, desmoid-type fibromatosis, PEComa, inflammatory myofibroblastic tumor, spindle cell squamous cell carcinoma, mucosal melanoma, monophasic synovial sarcoma, angiosarcoma, and spindle cell rhabdomyosarcoma. The single most important discriminator between all of these lesions and EBV-associated smooth muscle tumors is the presence of nuclear EBER. Therefore, including an EBER in situ hybridization study when reviewing primitive or spindled cell tumors in the larynx would greatly aid in reaching a diagnosis. It is important to exclude a spindle cell squamous cell carcinoma, as these tumors most frequently present as a polypoid mass in the larynx. Further, it is well known that epithelial markers may be absent and co-expression of SMA can be seen [44–46]. However, the lack of surface involvement, and the absence of p40, p63, and CK5/6 reactivity, with a much stronger SMA, SMMHC and H-caldesmon are able to assist in the separation of smooth muscle tumors from squamous cell carcinoma. Monophasic synovial sarcoma are typically hypopharyngeal tumors, not associated with immunosuppression, and usually show EMA and TLE1 by immunohistochemistry, with coexpression of SMA in some tumors [25]. An inflammatory myofibroblastic tumor is often in young adults, showing a mixture of inflammatory cells with myofibroblastic cells, the latter frequently giving a ganglion cell-type appearance. Tumors are commonly ALK immunopositive, but a significant subset, especially in older patients, are ALK negative, while still showing muscle marker reactivity [30, 47–50]. Spindle cell melanoma usually shows prominent nucleoli, intranuclear cytoplasmic inclusions, and cytoplasmic pigmentation, with a strong reaction with SOX10, S100 protein, HMB45, and/or Melan-A, while lacking muscle markers [51–53]. An angiosarcoma shows freely anastomosing vessels, neolumen formation, extravasated erythrocytes, and demonstrates reactivity with vascular markers (ERG, FLI1, CD34, CD31, D2-40), which are not seen in smooth muscle tumors [54]. A rhabdomyosarcoma could be similar, but tends to have tumor necrosis, and demonstrates desmin, myogenin, MYO-D1, and myosin immunoreactivity. Peripheral nerve sheath tumors (benign or malignant) usually show S100 protein and/or SOX10 reactivity, which is not seen in EBV-associated smooth muscle tumors. PEComa usually shows cleared cells and tends to be a neck tumor, rather than laryngeal mass, with both desmin and HMB45 immunoreactivity [10, 55, 56]. Desmoid-type fibromatosis affects the neck, rather than larynx, and demonstrates a much more hypocellular proliferation, with collagen deposition and nuclear ß-catenin immunoreactivity [57–60]. A solitary fibrous tumor shows more buckled or wavy nuclei, dense, keloid-like collagen deposition, and is strongly immunoreactive with STAT6 [32].

One of the unique findings in larynx EBV-associated smooth muscle tumors is a more primitive or round cell appearance, along with a relatively increased mitotic rate in a tumor that does not show necrosis or pleomorphism. Thus, it is probably prudent in head and neck smooth muscle tumors to perform EBER for mucosal site primaries, just to exclude the association. Further, obtaining clinical information about a history of immunosuppression for any reason would also aid in interpretation, and potentially influence management. Association with Li-Fraumeni syndrome and radiation exposure is not documented for EBV-associated tumors, even though identified as a predisposing factor in other head and neck smooth muscle tumors (especially leiomyosarcomas) [10].

Prognosis is mainly dependent on the condition of the individual patient's immune system, but nearly all of the reported cases in the larynx (and other head and neck sites) show an indolent behavior, managed by limited surgery, without development of metastatic disease. Still, as many of the cases may be part of multifocal disease, close clinical follow-up is required to detect development of a new tumor. In the 12 reported patients, 3 have died; 2 with disease at 48 and 108 months, while the other patient died at 105 months without disease. Of the remaining 9 patients who are alive, two have evidence of disease at 20 and 60 months of follow-up respectively. However, none of the reported patients have developed metastatic disease or recurrence locally, even when part of multifocal disease. Still, follow-up is an

average of 44.8 months for all patients, and 37.6 months for those who are still alive, and thus is a relatively short duration. Still, based on current findings, it seems that EBV-associated smooth muscle tumors of the larynx can be managed conservatively with local excision, without radical resection or follow-up radiation or chemotherapy. Ten of the reported patients had conservative management, with only two patients treated with follow-up radiation therapy.

Conclusions

EBV-associated smooth muscle tumors may be seen in the larynx and other head and neck organ sites. The clinical information about patient immunocompromise must be actively sought and documented, with kidney transplantation a common reason for immunocompromise. The tumors have a polypoid appearance grossly and can be removed conservatively without radical resections. The histologic features are characteristic of smooth muscle tumors, although frequently showing alternating light and dark areas which match the low power cellularity, with areas of a "round-cell" pattern noted. Mitotic figures may be increased (median 9/2 mm^2), but without atypical forms, tumor necrosis, or significant pleomorphism, leiomyosarcoma should not be diagnosed. The neoplastic cells are highlighted with SMA, H-caldesmon, smooth muscle myosin heavy chain, and EBER by in situ hybridization, the latter a critical study in confirming the diagnosis.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest as it relates to this research project.

Ethical approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of Southern California Permanente Medical Group.

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