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Clinical Record

Epstein–Barr virus-associated smooth muscle tumour mimicking bilateral vocal process granuloma

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Abstract

A case is presented of a 36-year-old Chinese woman with a renal transplant for end-stage renal failure due to Goodpasture's syndrome. She presented with a year's history of throat discomfort and acid regurgitation into her throat. Videolaryngoscopy revealed bilateral vocal process granuloma, presumed to be due to gastroesophageal reflux. A four-week course of high dose omeprazole was prescribed. On follow up a month later, the granulomas had enlarged, and laser excision was undertaken. Histological and immunohistochemical staining was consistent with Epstein–Barr virus-associated smooth muscle tumour. This is believed to be the first reported case in the English literature of such a tumour affecting the vocal process. The aim of this paper is to present the pathogenesis, clinical behaviour and treatment of Epstein–Barr virus-associated smooth muscle tumour, and to review the literature concerning the differential diagnosis of polypoid vocal process lesions.

Key words: Epstein Barr virus; smooth muscle tumour; larynx immunocompromised; granulomas; vocal process

Introduction

Epstein–Barr virus (EBV) is a double-stranded deoxyribonucleic acid enveloped virus belonging to the herpes virus family. It is associated with lymphomas, nasopharyngeal carcinomas, human immunodeficiency virus-associated and post-transplant lymphoproliferative disorders.[1] Epstein–Barr virus-associated smooth muscle tumour is a smooth muscle tumour characterised by the presence of EBV-encoded ribonucleic acid (RNA) in smooth muscle cells.[2] It usually exhibits little atypia and low levels of mitotic activity.[2] Little is known of the natural history of this rare disorder, but the condition seems to improve with modification and reduction of the immunotherapy dose. The tumour has been reported to occur in the lung, kidney, liver, spleen, dura and skull base.[2,3] However, the current report is believed to be the first published case in the English literature of EBV-associated smooth muscle tumour affecting the vocal process.

Case report

A 36-year-old Chinese lady was diagnosed in September 1986 with end-stage renal failure as a result of Goodpasture's syndrome. She received continuous ambulatory peritoneal dialysis, but this was complicated by methicillin-resistant *Staphylococcus aureus* peritonitis in May 1990. As a result, she was placed on haemodialysis for one year before receiving a cadaveric renal transplant in March 1992. Post-transplantation, she received cyclosporine, azathioprine and prednisolone for immunosuppression.

The patient was referred to the Ear, Nose and Throat Centre at Singapore General Hospital in May 2005 with a one-year history of throat discomfort associated with regurgitation of acid into her throat at night. She denied dysphagia, odynophagia or hoarseness of voice.

Videolaryngoscopy revealed what appeared to be bilateral vocal process granulomas (Figure 1). In view of the patient's history of acid regurgitation and coexisting signs of posterior laryngeal and subglottic oedema, these granulomas were presumed to be a result of gastroesophageal reflux. She received a four-week course of high dose proton pump inhibitor (40 mg omeprazole twice daily).

On follow up a month later, the patient's symptoms persisted and the vocal process lesions had increased in size (Figure 2). Subsequently, she underwent laser excision of the lesions.

Histological examination was consistent with Epstein–Barr virus (EBV) associated smooth muscle tumour. The polypoid tissue was covered by squamous epithelium, associated with a proliferation of spindle cells resembling smooth muscle cells arranged in fascicles (Figure 3). On immunohistochemical analysis, the spindle cells stained for smooth muscle actin (Figure 4) and vimentin. Focal staining was seen with caldesmon. Staining for desmin, S-100, epithelial membrane antigen (EMA), leucocyte common antigen (LCA), CD34, CK19, AE1/3 and CD99 were negative. In situ hybridisation for EBV-encoded RNA was focally positive (Figure 5).

A computed tomography (CT) scan of the thorax was ordered in view of the patient's long-standing dry cough and suspicion of a lymphoproliferative disorder in the setting of immunosuppression. The CT showed bilateral, subcentimeter lung nodules suggestive of metastatic disease or lymphoproliferative disorder (Figure 6). The patient refused biopsies of the pulmonary nodules. Her azathioprine and cyclosporine prescriptions were discontinued and replaced with sirolimus.

At out-patient follow up, two weeks following surgery, the patient's symptoms had subsided. Nasoendoscopy showed that the vocal process wounds were healing well. A follow-up CT scan of the thorax, three months after surgery, showed no

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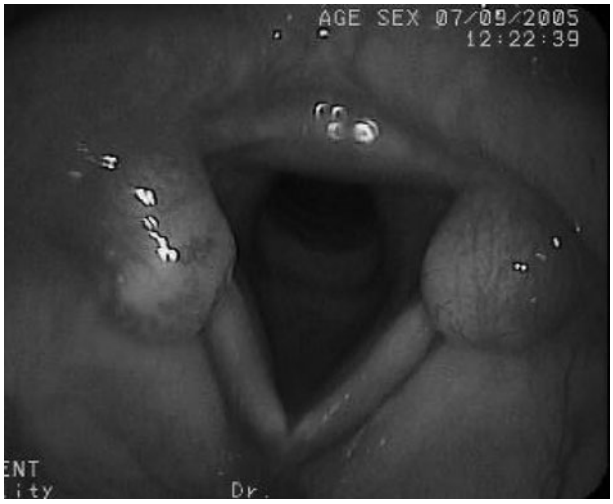

FIG. 1

Videolaryngoscopic view of presumed bilateral vocal process granulomas (first presentation). Note also the presence of posterior laryngeal and subglottic oedema, suggestive of gastroesophageal reflux disease.

progression of the lung lesions. Further nasoendoscopic evaluation five months after surgery showed no recurrence of the vocal process lesions (Figure 7).

Discussion

Epstein–Barr virus-associated smooth muscle tumour is a recently identified entity that occurs in immunocompromised patients. The association between post-transplant spindle cell tumour and Epstein–Barr virus (EBV) was first described by Lee *et al.* in 1993.[4] In a 2002 literature review by Cheuk *et al.*, 46 cases of EBV-associated smooth muscle tumour were identified from various sites. The liver, gastrointestinal tract and lung were the most commonly involved locations.[3] However, to date, EBV-associated smooth muscle tumour has not been reported in the vocal process or larynx. Epstein–Barr virus-associated smooth muscle tumour has been found

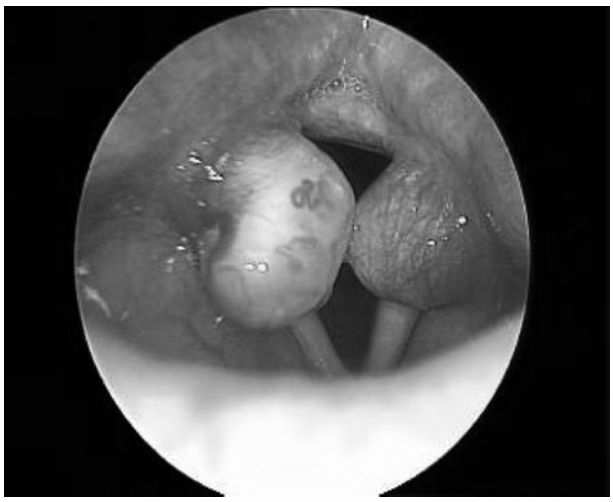

FIG. 2

Videolaryngoscopic view of bilateral vocal process 'granulomas' which have enlarged despite one month's treatment with high dose omeprazole.

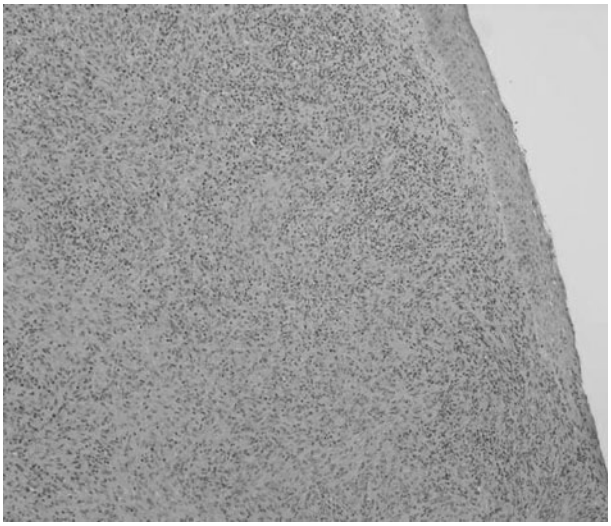

FIG. 3

Medium power photomicrograph of vocal fold biopsy, revealing a proliferation of spindle cells within the stroma, accompanied by a lymphoplasmacytic infiltrate (H&E; original magnification ×100).

to affect three groups of immunocompromised patients: those with acquired immunodeficiency syndrome (AIDS), organ transplantation recipients and those with severe congenital immunodeficiency.[3] In post-transplant patients, there seems to be a preponderance for the liver. The time of discovery of the tumour has varied from 1.25 to 66 months post-transplantation.[3] The majority of cases have occurred in children and adolescents, but this could be due to the age prevalence of the AIDS and transplant recipient patients in the series described.

The pathogenesis of EBV-associated smooth muscle tumour remains unclear due to the rarity of this condition. It has been hypothesised that high viral titres in immunocompromised patients allow tissues such as smooth muscle, which are normally resistant to infection under normal physiological conditions, to become infected.[5]

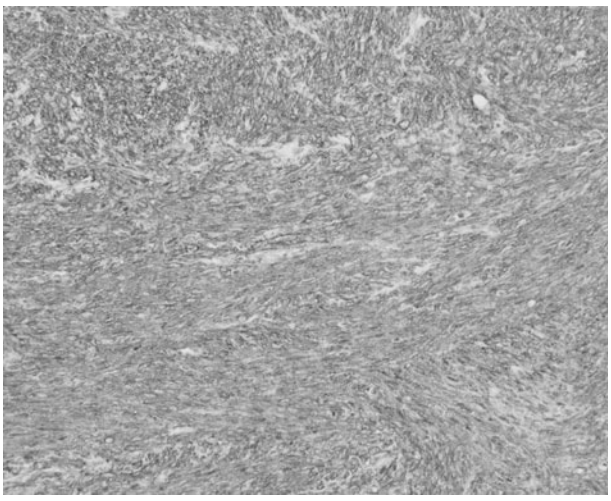

FIG. 4

Immunohistochemical photomicrograph showing spindle cells with positive staining for antibodies against smooth muscle actin, indicating smooth muscle differentiation (Avidin biotin complex; original magnification ×200).

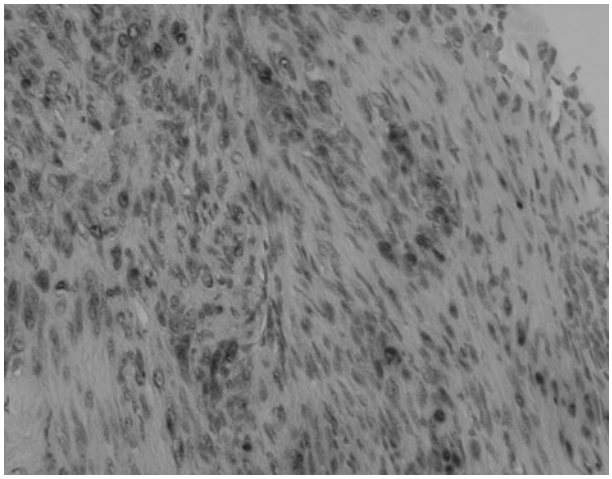

FIG. 5

On in-situ hybridisation, spindle cell nuclei were labelled by probes against Epstein–Barr virus encoded ribonucleic acid (peptide nuclei acid (PNA) detection kit; original magnification ×400).

Viral infection precedes clonal expansion of smooth muscle cells, and the presence of EBV monoclonality in these tumours suggests a primary role of EBV in tumorigenesis.[6] The current understanding of the ability of EBV to promote cell growth is derived mainly from *in vitro* studies of EBV-transformed B-lymphocyte cell lines.[7] Epstein–Barr virus gains entry into lymphoid cells via a transmembrane glycoprotein receptor known as CD21.[8] This receptor has been found in high levels in immunocompromised paediatric patients with leiomyomas and leiomyosarcomas.[9] The route of EBV entry into smooth muscle cells is unknown, although up-regulation of CD21 receptors has been shown.[6] Once within the myocytes, EBV maintains itself in three latency states, depending on the type of antigens expressed.[8] Epstein–Barr virus-associated smooth muscle tumour and post-transplant lymphoproliferative disorder typically exhibit EBV type III latency with the expression of EBV nuclear antigen 2 and latent membrane protein 1.[3] On the other hand, EBV type I latency is seen in Burkitt's lymphoma, while EBV type II latency is seen in Hodgkin's disease and nasopharyngeal carcinoma.[3]

The biological behaviour of EBV-associated smooth muscle tumour does not seem to correlate with its histological features. Tumours classified as benign or of uncertain malignant potential have been seen to behave aggressively,

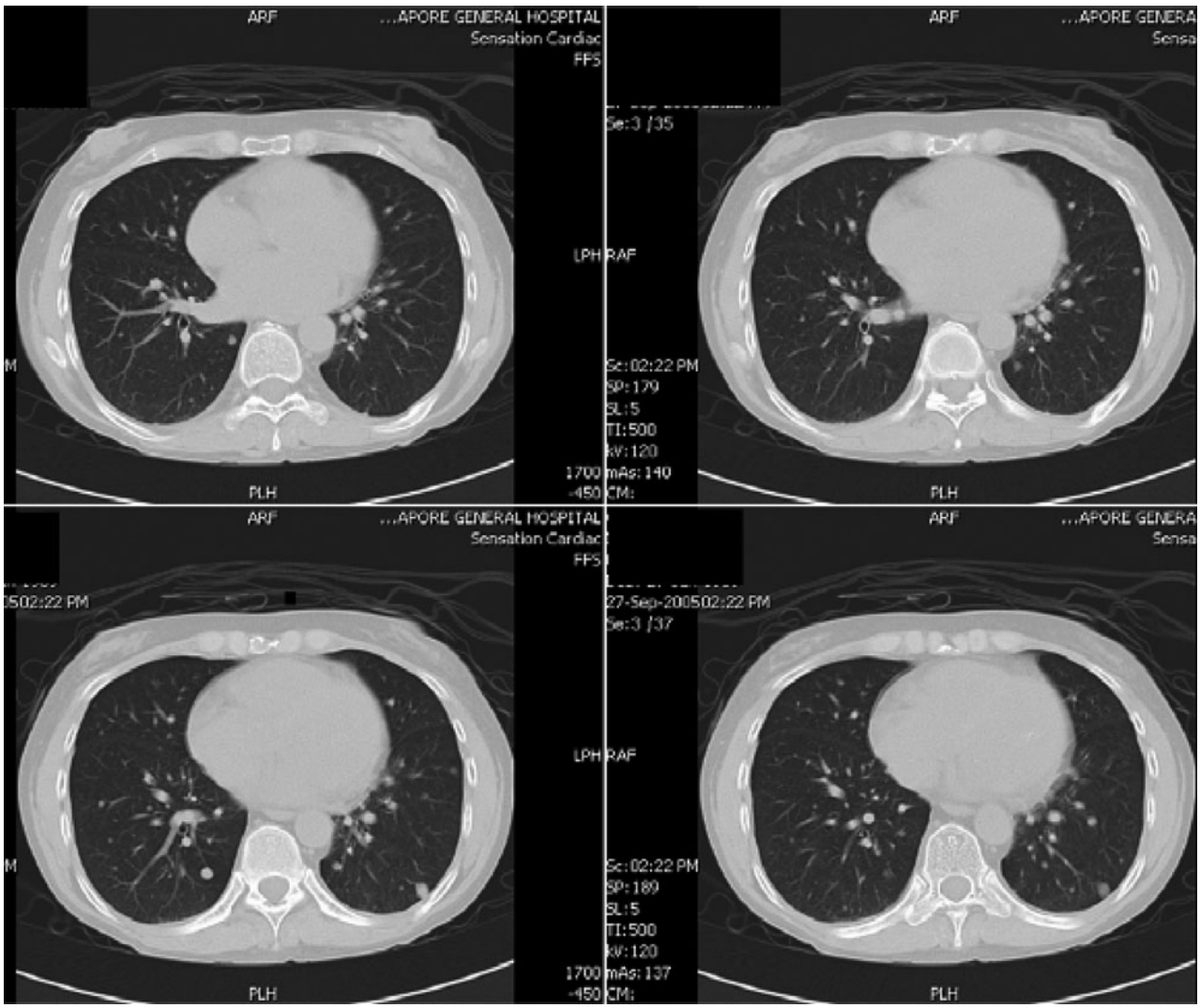

FIG. 6

Axial computed tomography scans of the thorax, showing multiple subcentimeter pulmonary nodules.

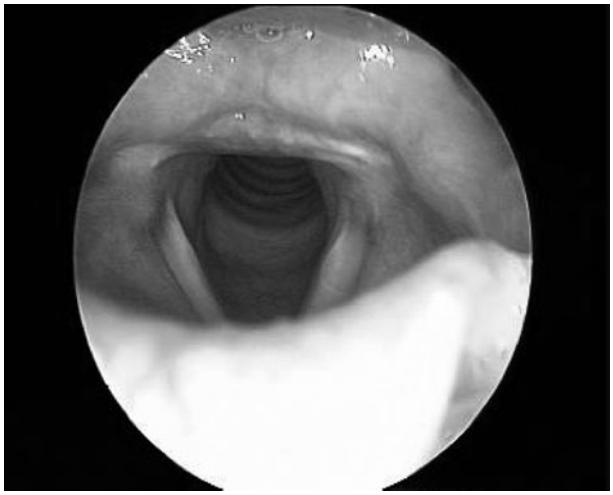

FIG. 7
Videolaryngoscopic view of the vocal processes five months after surgical resection, showing no recurrence of the lesions.

with multiorgan involvement and death in at least one case despite aggressive chemotherapy.[6] In our patient, multiple subcentimetric bilateral pulmonary nodules were seen. The patient refused biopsy, but, in the setting of immunosuppression, likely possible causes of the pulmonary nodules would be EBV-associated smooth muscle tumour or lymphoproliferative disorders. Epstein–Barr virus-associated smooth muscle tumour has been shown to involve more than one location in the same individual.[2,3,6,10] In a study of 19 patients by Deyrup *et al.* in 2006, 13 (68 per cent) were reported to have multiple tumours.[2] These authors found that multiple tumours in the same patient were clonally distinct, and they concluded that these tumours were the result of multiple infection events rather than metastasis.[2] There is no consensus on the standard treatment of EBV-associated smooth muscle tumour, although reduction or discontinuation of immunosuppression, with resultant tumour shrinkage, and surgical resection leading to cure have been reported in a few cases.[1,6,11]

The clinical presentation of EBV-associated smooth muscle tumour depends on the site of involvement. In this patient, EBV-associated smooth muscle tumour mimicked the appearance of bilateral vocal process granulomas, which were presumed to be due to gastroesophageal reflux. Vocal process granulomas or contact granulomas are benign, inflammatory lesions located at the cartilaginous part of the posterior glottis.[12,13] Proposed mechanisms for their formation include mechanical causes (such as vocal abuse, intubation injury and surgical trauma) and inflammatory causes (such as gastroesophageal refux, infection, postnasal drainage and allergy).[14]

The current management of contact granulomas is directed mainly at the multifactorial aetiology and includes speech therapy, lifestyle modification and antireflux measures.[15] Surgical resection of vocal process granuloma is usually avoided, as the recurrence rate after surgery is high (92 per cent).[16] Treatment should be aimed at removing chronic irritants leading to granuloma formation.[15] Indications for surgery include airway obstruction from large granulomas, diagnostic doubt and failed conservative treatment.[15] In our patient, failed response to high dose antireflux medication and an increase in size of the lesions led to surgical excision to obtain a histological diagnosis.

Other pathologies can mimic vocal process granulomas. In 1949, New and Devine reported three cases in which presumed vocal process granulomas were variously histologically identified as myxomatous tissue, haemangioendothelioma and squamous cell carcinoma.[17] In addition, in 1990 Wenig and Heffner reported 105 cases that had been diagnosed histologically as contact ulcers and sent for review at the Armed Forces Institute of Pathology. Their review reported histological misdiagnoses including pyogenic granuloma, haemangioma, haemangiopericytoma, Kaposi's sarcoma, angiosarcoma, spindle cell carcinoma and granulomatous infectious diseases.[18] The percentage of misdiagnoses was not available.

- **This is a case report of an immunocompromised patient who presented with granulomas over the vocal processes of the vocal folds**
- **The masses were thought initially to be due to reflux**
- **Subsequent analysis showed that they were smooth muscle tumours due to Epstein–Barr virus**
- **The literature surrounding such lesions is reviewed**

Bilateral vocal process granulomas are less prevalent than unilateral granulomas.[16,19] In Ylitalo and Lindestad's retrospective study of 120 patients with contact granulomas, only seven cases were bilateral.[16] Jaroma *et al.* reported 10 cases of bilateral vocal process granuloma in their series of 98 patients;[19] the histology of these bilateral granulomas was not available. However, a search of the English literature (via the Pubmed and MEDLINE databases) revealed one reported case of bilateral vocal process granuloma with a histological diagnosis of squamous cell carcinoma.[20]

Conclusion

Epstein–Barr virus-associated smooth muscle tumour is a rare condition that can mimic the appearance of vocal process granulomas in immunocompromised patients. It should be considered in the differential diagnosis when granulomas in such patients persist despite a period of medical and speech therapy. Bilateral granulomas are not common, and further studies would be needed to determine common aetiologies, so that a management algorithm can be formulated to optimise treatment.

References

1 Debriec-Rychter M, Croes R, De Vos R, Marynen P, Roskams T, Hagemeijer A *et al*. Complex genomic rearrangement of ALK loci associated with integrated human Epstein-Barr virus in a post-transplant myogenic liver tumor. *Am J Pathol* 2003;**163**:913–22
2 Deyrup AT, Lee VK, Hill CE, Cheuk W, Toh HC, Kesavan S *et al*. Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. *Am J Surg Pathol* 2006;**30**: 75–82
3 Cheuk W, Li PC, Chan JK. Epstein-Barr virus associated smooth muscle tumour: a distinctive mesenchymal tumour of immunocompromised individuals. *Pathology* 2002;**34**:245–9
4 Lee E, Dickman P, Jaffe R, Alashari M, Tzakis A, Reyes J. Post-transplant spindle cell tumor (PTST): an entity associated with Epstein Barr virus. *Mod Pathol* 1993;**6**:127A
5 Liebowitz D. Epstein-Barr virus – an old dog with new tricks. *N Engl J Med* 1995;**332**:55–7
6 Lee ES, Locker J, Nalesnik M, Reyes J, Jaffe R, Alashari M *et al*. The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation. *New Engl J Med* 1995;**332**:19–25

7 Wang F, Gregory C, Sample C, Rowe M, Liebowitz D, Murray R *et al*. Epstein-Barr virus latent membrane protein (LMP1) and nuclear proteins 2 and 3c are effectors in phenotypic changes in B lymphomas: EBNA-2 and LMP1 cooperatively induce CD23. *J Virol* 1990;**64**: 2309–18
8 Morgello S, Kotsianti A, Gumprecht JP, Moore F. Epstein-Barr virus-associated dural leiomyosarcoma in a man infected with human immunodeficiency virus. *J Neurosurg* 1997;**86**:883–7
9 McClain KL, Leach CT, Jenson HB, Joshi VV, Pollock BH, Parmley RT *et al*. Association of Epstein-Barr virus with leiomyosarcomas in young people with AIDS. *N Engl J Med* 1995;**332**:12–18
10 Boman F, Gultekin H, Dickman PS. Latent Epstein-Barr virus infection demonstrated in low grade leiomyosarcomas of adults with acquired immunodeficiency syndrome, but not in adjacent Kaposi's lesion or smooth muscle tumors in immunocompetent patients. *Arch Pathol Lab Med* 1997;**121**:834–8
11 Creager AJ, Maia DM, Funkhouser WK. Epstein-Barr virus-associated renal smooth muscle neoplasm: report of a case with review of the literature. *Arch Pathol Lab Med* 1998;**122**:277–81
12 Benjamin B, Croxson G. Vocal cord granulomas. *Ann Otol Rhinol Laryngol* 1985;**94**:538–41
13 Holinger PH, Johnston KC. Contact ulcers of the larynx. *JAMA* 1960;**172**:511–15
14 Hoffmann HT, Overholt E, Karnell M, McCulloch TM. Vocal process granuloma. *Head Neck* 2001;**23**:1061–74
15 Havas TE, Priestley J, Lowinger DS. A management strategy for vocal process granulomas. *Laryngoscope* 1999;**109**:301–6
16 Ylitalo R, Lindestad PA. A retrospective study of contact granuloma. *Laryngoscope* 1999;**109**:433–6
17 New GB, Devine KD. Contact ulcer granuloma. *Ann Otol Rhinol Laryngol* 1949;**58**:548–58
18 Wenig BM, Heffner DK. Contact ulcers of the larynx: a reacquaintance with the pathology of an often underdiagnosed entity. *Arch Pathol Lab Med* 1990;**114**:825–8
19 Jaroma M, Pakarinen L, Nuutinen J. Treatment of vocal cord granuloma. *Acta Otolaryngol (Stockh)* 1989;**107**:296–9
20 Sidle DM, Haines GK 3rd, Altman KW. Bilateral vocal process papillomas: report of a case. *Ear Nose Throat J* 2002;**81**:790–1

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