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导读：

喉腺鳞癌在组织学上同时存在腺癌和鳞癌两种成分，临床罕见，恶性程度高，预后较差。既往相关研究较少，多为单个病例报道。本文作者既往已对喉部非鳞状细胞恶性肿瘤做了大量总结，该文通过临床资料的汇报，并结合文献对喉腺鳞癌的病理、治疗和预后进行了相对全面的探讨，对临床上喉腺鳞癌的诊治有指导意义。

董　频

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Adenosquamous Carcinoma of the Larynx: A Case Report and Literature Review

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[**Abstract**] **Objective**: To retrospectively analyze the clinical characteristics of laryngeal adenosquamous carcinoma (ASC) and review the related literature. **Methods**: We retrospectively analyzed five male patients with confirmed ASC of the larynx between 2005 and 2010 in our hospital, accounting for 0.2% of the laryngeal malignant tumors in the same period. **Results**: All patients underwent surgeries including horizontal partial laryngectomy (2 cases), vertical partial laryngectomy (1 case) and total laryngectomy (2 cases). One of the two who underwent total laryngectomy also received post-operative chemoradiotherapy. Four also underwent neck dissections. The mean follow-up time was 77.4 ± 14.98 months. At the end of follow-up, two suffered regional metastasis and another local relapse. They all underwent related operations again and were still alive. The therapeutic approach might follow that of squamous cell carcinoma of the larynx. **Conclusion**: Our limited cases suggest that the prognosis of adenosquamous carcinoma of the larynx is similar to that of squamous cell carcinoma of the larynx.

[**Key words**] Laryngeal neoplasm; Adenosquamous carcinoma; Histopathology; Clinical protocol

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INTRODUCTION

Adenosquamous carcinoma (ASC) of the head and neck is a rare entity; it is a malignant tumor with histological features of both a true adenocarcinoma and a squamous cell carcinoma. It was first described by Gerughty et al in 1968 in a series of 10 patients, with fewer than 100 cases reported in the English language literature to date. The larynx is the most common site of involvement within the head and neck[1-2]. Accord-

ing to the literature, ASC is an aggressive malignant neoplasm with a poor prognosis, characterized by local recurrence, early cervical lymph node metastasis, and distant dissemination[3-4]. However, its histogenesis, treatment, and prognosis remain controversial. To further understand the clinicopathological features of this unusual tumor, we present five cases of ASC of the larynx and describe the clinical characteristics with an emphasis on an improved prognosis.

METHODS

Five cases of ASC of the larynx treated between January 2005 and December 2010 were identified from the files in otolaryngology and pathology departments of Eye & ENT Hospital of Fudan University. This retrospective clinical study has been approved by Ethics Committee of Eye & ENT Hospital of Fudan University. Clinical information regarding the presentation, pathology, treatment, and outcome was obtained from a review of patient charts. The follow-up time until last contact was determined for all patients. Hematoxylin and eosin (HE) and immunohistochemically stained slides were reviewed and confirmed in all cases by two experienced pathologists.

RESULTS

Patient demographics

Five males with ASC of the larynx were evaluated (Table 1). The mean age at diagnosis was 62.6 ± 6.58(55 – 72) years. The mean course of the disease was 2 months. Three of the five patients had a tobacco history, and none admitted alcohol addiction or a history of exposure to environmental carcinogenic substances. The presenting complaints included hoarseness, pharyngalgia and odynophagia. According to the tumor-node-metastasis (TNM) staging system developed by the American Joint Committee on Cancer, the patients' tumors were in stages II ($n = 1$), III ($n = 3$) and IVa ($n = 1$).

Table 1. Clinical Characteristics of 5 Cases of Adenosquamous Carcinoma of the Larynx

Case	Age*/sex	Smoking history	Presentation	Tumour site	TNM classification	Initial treatment	Recurrence/ treatment	Follow-up+ /status
1	55/M	Yes	Hoarseness	Epiglottis, left false vocal cord	$T_2N_0M_0$	HPL + SND	Regional/ RND	96/AWD
2	72/M	No	Hoarseness	Bilateral vocal cords	$T_3N_0M_0$	TL + SND	No	75/AWOD
3	58/M	Yes	Pharyngalgia	Epiglottis, left false vocal cord	$T_2N_1M_0$	HPL + SND	Regional/ RND	67/AWD
4	65/M	No	Hoarseness	Right vocal cord	$T_3N_0M_0$	VPL	Local/TL	60/AWOD
5	63/M	Yes	Odynophagia	Epiglottis, left aryepiglottic fold	$T_3N_2M_0$	TL + RND + CRT	No	89/AWOD

* Year; + Month.

HPL: Horizontal partial laryngectomy; SND: Selective neck dissection; RND: Radical neck dissection; AWD: Alive with disease; TL: Total laryngectomy; AWOD: Alive without disease; VPL: Vertical partial laryngectomy; CRT: Chemoradiotherapy.

Diagnosis and pathology

ASC of the larynx was diagnosed after the initial biopsy of the neoplasm by operative microlaryngoscopy, and was confirmed after complete resection. Histopathologically, the tumors exhibited features of both adenocarcinomas and squamous cell carcinomas (Figure. 1).

Treatment and follow-up

The five patients underwent various surgeries with curative intent (Table 1). The therapeutic principles followed those for squamous cell carcinoma of the larynx. One patient received post-operative chemoradiotherapy.

The average length of follow-up was 77.4 ± 14.98 (60-96) months. At the time when this case report was written, the five patients were alive and being followed; two suffered ipsilateral cervical lymph node metastasis and underwent a radical neck dissection, and

one suffered local recurrence and received a total laryngectomy. No patient had distant metastasis.

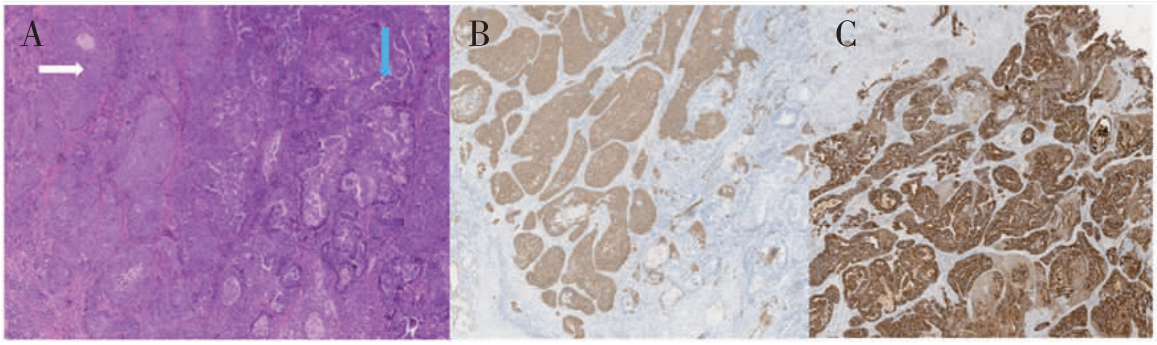

Figure 1. Pathological Characteristics of Adenosquamous Carcinoma of the Larynx (40 × Magnification)

A: HE stain showed the adenocarcinoma component (as indicated by the blue arrow) and squamous cell carcinoma component (as indicated by the white arrow); B: Immunodetection of squamous cell carcinoma marker (CK5/6); C: Immunodetection of adenocarcinoma marker (CK7).

DISCUSSION

ASC of the larynx is an extremely rare, malignant tumor with both squamous cell carcinoma and adenocarcinoma components[5-7]. The histogenesis of ASC is still controversial, although it is becoming more accepted that ASC of the head and neck originates from the mucosal epithelium of the upper respiratory tract[2]. A strong male predilection is observed, with a high incidence during the 6th and 7th decades of life[8]. The larynx is the most common site of origin (almost 50%) in the upper aero-digestive tract, with the supraglottis as the preferred subsite[3]. In our series, five male patients were confirmed with ASC of the larynx in our hospital between 2005 and 2010, accounting for 0.2% of the laryngeal malignant tumors in the same period. The mean age at diagnosis was 62.6 ± 6.58 years. Three tumors were located in the supraglottis and two in the glottis (one tumor per capita).

A definitive diagnosis of ASC depends on the histological and immunohistochemical identification of squamous and glandular components in close proximity but in generally distinct areas, although mixed areas or confluence areas may also exist[9-10]. Generally, the squamous cell carcinoma component was observed most commonly in the superficial part of the tumor, which can be in situ or invasive and ranges from well to poorly differentiated[11]. The adenocarcinoma, in turn, tends to occur in the deeper part of the tumor, which can have a tubular, alveolar, and/or glandular morphology[12]. The majority of the tumors are moderately differentiated, with the squamous cell carcinoma component in predominance. Immunohistochemical evaluation was performed and showed a squamous and glandular differentiation. In this study, squamous cell carcinoma marker CK5/6 and adenocarcinoma marker CK7 were assayed (Figure 1. B, Figure 1. C). Because of its peculiar characteristics, the exact diagnosis may only be established after assessment of the completely resected specimen. Sheahan et al suggested that ASC may be more common than reported in the published data, given that many cases may have been missed, particularly when diagnoses are made on the basis of small biopsies or when one of the components predominates over the other[13]. This may also explain that why most patients were in advanced stage at the time of diagnosis.

Typically, it has been reported that ASC of the head and neck is an extremely aggressive neoplasm, characterized by local recurrence, cervical lymph node metastasis, and distant dissemination, with the lung as the most common site, and a poor long-term prognosis[14-15]. In a review of 58 cases of ASC of the head and neck, Keelawat et al reported 46.7% of local recurrences, 64.7% of regional metastases, and 23.1% of distant dissemination. The 3-, 5- and 10-year survival rates were 32.1%, 13% and 4.5%, respectively, with 42.9% of patients died of their disease at a mean follow-up period of 24.7 months[16]. These findings were from an investigation of all head and neck sites, including the larynx, oral cavity, nasal cavity/paranasal sinuses, and pharynx. We reviewed ASC of

the larynx that were included in the three largest English-language reports (Table 2)[12,16-17]. There were 15 cases of ASC of the larynx with sufficient follow-up data, in which stage I (2/15), II (5/15), III (1/15), and IV (7/15) cancer patients were reported. The prognosis was obviously different between stages I-II and stages III-IV, with 6 stage I-II (6/7) and 1 stage III-VI (1/8) cancer patients alive. These results confirmed the correlation between the outcome and the stage of the tumor, and at the same time, suggested that ASC of the larynx had a slightly better prognosis than that of other sites in the head and neck. For example, Passon et al reported a patient with a T2N0M0 ASC of the supraglottis who had a 15-year disease-free survival[3]. In our series, all five patients (stage II, $n=1$; stage III, $n=3$; stage IV, $n=1$) were alive during the follow-up period, although three had experienced regional/local recurrence. Some authors have attributed this to the relatively sparse lymphatic drainage of the larynx compared to other head and neck sites, although there are few reports of longer survival of ASC arising in other head and neck sites[2,18].

Little is known about the factors affecting prognosis, mainly because of the condition's rarity and the lack of any large, controlled studies. Our series was too small to reach any valuable conclusion about prognosis, except that the patients seemed to have better prognoses than those in most other reports. Indeed, most authors have suggested that the higher the stage, the worse the prognosis, thus demonstrating a worse prognosis in stages III and IV cancer patients than in stages I and II cancer patients[16,19]. However, it is still important to investigate various factors that affect prognosis, including perineural invasion, node status (N), human papillomavirus status, the degree of tumor differentiation, and the proportions of the glandular and squamous components in the tumor[20-22].

No treatment has been standardized, again because of the condition's rarity. Most authors recommend early and aggressive surgical resection for the treatment of ASC in the head and neck, which includes a wide local excision and neck dissection, even in the absence of clinically evident lymph node metastases[23]. In fact, for ASC of the larynx, we suggest that the primary mode of treatment should be surgery, with the choice of surgical method and the application of postoperative radiotherapy/radiochemotherapy in accordance with the laryngeal squamous cell carcinoma[24-26]. In our series, two suffered regional metastasis, and one local relapse at the end of follow-up. Among them, two cases with regional metastasis survived with tumor after salvage surgery, indicating that comprehensive treatment, especially postoperative radiotherapy/radiochemotherapy may be very important.

Table 2. ASC of the Larynx Included in the Three Largest English-Language Reports

Case	Keelawat et al.			Masand et al.			Alos et al. Case		
	Sex/age	Stage	Follow-up	Sex/age	Stage	Follow-up	Sex/age	Stage	Follow-up
1	F/64	III	N/A	M/59	IV	DOD/8	M/48	IV	AWOD/54
2	M/72	IV	DOD/11	M/43	II	AWOD/128	M/58	II	DOD/35
3	M/56	IV	DOD/33	M/60	II	AWOD/54	M/70	IV	DOD/21
4	M/81	III	DOD/31	M/69	IV	DOD/1.5	M/66	II	AWD/36
5	F/72	IV	DOD/11	M/51	I	AWOD/42	M/61	I	AWOD/60
6				M/66	II	AWD/26			
7				M/58	IV	N/A			

DOD: Dead of disease; AWOD: Alive without disease; AWD: Alive with disease.

CONCLUSIONS

ASC of the larynx is a very rare tumor, but the larynx is the most common site of involvement within the head and neck. It is characterized pathologically by the simultaneous presence of squamous cell carcinoma and adenocarcinoma. The therapeutic approach might follow that of squamous cell carcinoma of the larynx. Clinically, our limited cases suggest that the prognosis of ASC of the larynx is similar to that of squamous cell carcinoma of the larynx. Further investigations and more detailed data are needed to fully understand the

clinical characteristics of ASC of the larynx.

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