Undifferentiated Laryngeal Carcinoma with Pagetoid Spread

Sulen Sarioglu¹ · Ersoy Dogan² · Yasemin Sahin¹ · Evren Uzun¹ ·
Recep Bekis³ · Emel Ada⁴ · Ozgul Sagol¹ · Fadime Akman⁵

Received: 4 June 2015 / Accepted: 11 August 2015 / Published online: 21 August 2015
© Springer Science+Business Media New York 2015

Abstract Pagetoid spread, is used to define intraepithelial spread of cancer cells, when a massive carcinoma is identified beneath the basal membrane. There are only few reports of pagetoid spread at the head and neck region. Herein a 74 year old male patient with bilateral transglottic laryngeal high grade malignant epithelial tumor with pagetoid spread is presented. The tumor was located at the submucosa and there was spread of the CK7 and CK19 positive tumor cells into the non neoplastic mucosa, which was CK5/6 positive, sparing the basement membrane, creating a typical pagetoid pattern. Radiographic and positron emission tomography scan examination of the patient was unremarkable at presentation other than the laryngeal and neck lesions; but extensive systemic metastasis developed at 6 months following operation. To the best of our knowledge no epithelial malignancy with pagetoid spread was described at the larynx. Pagetoid spread may be a hallmark of very aggressive behavior in laryngeal carcinoma.

Keywords Larynx · Undifferentiated carcinoma · Pagetoid spread · Aggressive behavior

There are only a few reports of pagetoid spread at the head and neck region. Herein a 74-year old male patient with bilateral undifferentiated transglottic laryngeal carcinoma with pagetoid spread is presented. The patient developed extensive systemic metastasis at 6 months following operation. Pagetoid spread may be an overlooked hallmark of very aggressive behavior in laryngeal carcinoma.

Introduction

Pagetoid spread is very rarely described in head and neck carcinomas and nearly all these cases are from the salivary gland origin. Of the three previously reported cases in the oral cavity, two cases were salivary duct carcinomas and one case was an adenocarcinoma [1–3]. Pagetoid spread was also described in a maxillary sinus salivary hybrid carcinoma with high-grade transformation [4]. Intraductal spread along the salivary gland duct was proposed as a mechanism of pagetoid spread for these tumors [2–4]. A nasal case with sebaceous carcinoma with pagetoid spread, originating from the nasolacrimal duct, was also described [5]. There is only one case located in the larynx with features of Pagetoid spread, which was diagnosed as an aggressive granular cell tumor in 1990 [6]. To the best of our knowledge, no epithelial malignancy with pagetoid spread has been described in the larynx.

Case Report

Laryngeal biopsy tissue block from right vocal cord was submitted to our department. The biopsy was obtained from a 74-year old male patient, previously diagnosed at

✉ Sulen Sarioglu
sulen.sarioglu@deu.edu.tr

¹ Department of Pathology, Faculty of Medicine, Dokuz Eylul University, 35340 Inciralti, Izmir, Turkey

² Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Dokuz Eylul University, Inciralti, Izmir, Turkey

³ Department of Nuclear Medicine, Faculty of Medicine, Dokuz Eylul University, Inciralti, Izmir, Turkey

⁴ Department of Radiodiagnostics, Faculty of Medicine, Dokuz Eylul University, Inciralti, Izmir, Turkey

⁵ Department of Radiation Oncology, Faculty of Medicine, Dokuz Eylul University, Inciralti, Izmir, Turkey

another center as poorly differentiated squamous cell carcinoma. The laryngoscopic and radiological examination of the patient revealed a predominantly right-sided bilateral transglottic mass with subglottic invasion and multiple lymph nodes at the neck. He had a 50 pack-year history of smoking and quit smoking 15 years ago. His medical history, physical examination and laboratory findings were otherwise unremarkable.

The biopsy revealed an undifferentiated submucosal carcinoma with both single and grouped tumor cells at the overlying mucosa, extending in a pagetoid fashion. The atypical tumoral cells, arranged in a solid pattern, were CK7 and CK19 positive and CK5/6, CK20, CDX2, GCDP15, PSAP, PLAP, TTF-1, s100, MELAN-A, HMB45, calcitonin, chromogranin-A, synaptophysin, p63, actin, vimentin, androgen receptor, c-erbB2 and EBER negative (Figs. 1, 2, 3). There was no keratinisation or gland formation, and mucin stains were negative. The diagnosis was undifferentiated carcinoma. Systematic physical and radiological evaluation as well as PET scan was unremarkable for the whole body excluding the right laryngeal region [(right first; SUVmax:9.1) and the neck region (right second; SUVmax:6.3 and right third; SUVmax:6.0)].

Total laryngectomy and right neck dissection were performed. Tumor morphology was similar to the biopsy. There was no connection between epithelial and submucosal involvement. The tumor was bilateral and transglottic with 14 mm subglottic invasion without extralaryngeal spread (pT3) (Fig. 4). There was lymphatic and perineural invasion as well as mucosal extensive pagetoid spread of the tumor cells and involvement of seromucinous ducts (Fig. 5). The tumor was more than 1 cm away from the left superior margin, however the tumor was positive at the mucosal epithelium, again spreading in a pagetoid fashion. The radical neck dissection included 55 lymph nodes, of which 10

Fig. 1 Undifferentiated carcinoma (H&E, original magnification $\times 40$)

Fig. 2 Cytokeratin 19 expression at the mucosa limited to the neoplastic cells spreading in a pagetoid fashion and the submucosal tumor (CK19, original magnification $\times 2$)

Fig. 3 Pagetoid spread of CK5/6 negative tumoral cells at the laryngeal mucosa (CK5/6, original magnification $\times 40$)

were metastatic (pN2b). Two of these had extranodal invasion. The patient received chemoradiotherapy (locoregional 60 Gy radiotherapy concomitantly with two cycle of cisplatin 75 mg/m²) following the operation.

During follow up at 6 months, lung, liver, abdominal lymph node, and bone metastases were observed on PET scan (Fig. 5). The liver biopsy was performed and revealed undifferentiated carcinoma with morphological and immunohistochemical findings identical to the laryngeal carcinoma.

Discussion

Paget's disease of the mammary gland is the extension of the neoplastic glandular cells into the nipple epidermis without the destruction of the basement membrane, mostly

Fig. 4 Predominantly right sided transglottic laryngeal carcinoma, total laryngectomy

Fig. 5 Pagetoid spread of tumoral cells at the laryngeal mucosa and excretory ducts (H&E, original magnification $\times 10$)

via the lactiferous ducts. It is considered to have a poor prognosis if there is an underlying carcinoma, which is the case in most of the patients [7, 8]. Extramammary Paget's disease is most frequently observed at the genital and perianal region [9].

Paget's disease is recognized by observation of malignant cells at the otherwise nonneoplastic epidermis or mucosal epithelium, frequently at the basal layer and sometimes spreading into the superficial layers either as single cells or clusters, sometimes forming glandular

structures [7–9]. Immunohistochemistry is helpful as the malignant cells present different expression of antigens from the non-neoplastic epithelial cells [9]. “Pagetoid spread” is used to define intraepithelial spread of cancer cells, when a massive carcinoma is identified beneath the basal membrane [3–7]. In the present laryngeal case, there was spread of the CK7 and CK19 positive tumor cells into the non neoplastic mucosa which was CK5/6 positive, sparing the basement membrane, creating a typical pagetoid pattern evidenced both by morphology and immunohistochemical staining. Pagetoid spread is a very rare entity in head and neck tumors and four cases were reported to the best of our knowledge [1–4], excluding the sebaceous carcinomas of the orbit and parotid gland [10]. Both the tumor type and the localization of present case seem to be different from the previous ones. However, as extensive sampling could not demonstrate the connection of the carcinoma with the mucosal epithelium, except for the salivary gland ducts, the possibility of an undifferentiated carcinoma arising from the laryngeal seromucous glands might be considered. The CK7 and CK19 expression are expected in salivary type tumors, reflecting ductal differentiation [11].

The differential diagnosis of the present tumor, with unique morphological features, included malignant melanoma with pagetoid spread which may rarely express keratins [12] and metastatic carcinoma. Immune profile as well as radiological and PET scan findings could not prove another primary site at presentation. Although most aggressive treatment protocols were applied, early distant spread of this high grade and stage neoplasm could not be prevented.

Conclusions

Undifferentiated carcinoma and pagetoid spread are exceptional findings in larynx, yet should not be overlooked, as these features may be the hallmarks of very aggressive behavior.

Acknowledgments The authors thank Prof. Aysun Uguz and Cukurova University Faculty of Medicine Department of Pathology, Turkey for evaluating androgen receptor expression.

Compliance with Ethical Standards

Conflict of interest Authors have no conflict of interest.

References

1. Changus GW, Yonan TN, Bartolome JS. Extramammary Paget's disease of the tongue. *Laryngoscope*. 1971;81(10):1621–5.

2. Theaker JM. Extramammary Paget's disease of the oral mucosa with in situ carcinoma of minor salivary gland ducts. *Am J Surg Pathol*. 1988;12(11):890–5.
3. Kikuchi Y, Uozaki H, Itoyama S, Saijo H, Takato T, Fukayama M. Pagetoid spread to oral mucosa from submandibular gland salivary duct carcinoma: a case report. *Hum Pathol*. 2009;40(7):1036–9.
4. Tran TA, Jennings T, Carlson JA. Dedifferentiated salivary hybrid carcinoma of the maxillary sinus with pagetoid spread to the overlying lining mucosa. *Head Neck Pathol*. 2015;9(2):293–9.
5. Shet T, Kelkar G, Juvekar S, Mistry R, Borges A. Masquerade syndrome: sebaceous carcinoma presenting as an unknown primary with pagetoid spread to the nasal cavity. *J Laryngol Otol*. 2004;118(4):307–9.
6. Brandwein M, LeBenger J, Strauchen J, Biller H. Atypical granular cell tumor of the larynx: an unusually aggressive tumor clinically and microscopically. *Head Neck*. 1990;12(2):154–9.
7. Lee HW, Kim TE, Cho SY, et al. Invasive Paget disease of the breast: 20 years of experience at a single institution. *Hum Pathol*. 2014;45(12):2480–7.
8. Ling H, Hu X, Xu XL, Liu ZB, Shao ZM. Patients with nipple-areola Paget's disease and underlying invasive breast carcinoma have very poor survival: a matched cohort study. *PLoS One*. 2013;8(4):e61455.
9. Lam C, Funaro D. Extramammary Paget's disease: summary of current knowledge. *Dermatol Clin*. 2010;28(4):807–26.
10. Wali UK, Al-Mujaini A. Sebaceous gland carcinoma of the eyelid. *Oman J Ophthalmol*. 2010;3(3):117–21.
11. Ilie M, Hofman V, Pedetour F, Attias R, Santini J, Hofman P. Oncocytic lipoadenoma of the parotid gland: Immunohistochemical and cytogenetic analysis. *Pathol Res Pract*. 2010;206(1):66–72.
12. Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. *Histopathology*. 2000;36(5):387–402.