

CASE REPORT

p16-positive oropharyngeal cancer with rare thyroid metastasis : A case report

Hidenori Suzuki¹, Eiichi Sasaki², Daisuke Nishikawa³, Daisuke Nishikawa¹, Yusuke Koide¹, Shintaro Beppu¹, Hoshino Terada¹, and Nobuhiro Hanai¹

¹Department of Head and Neck Surgery, ²Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan,

³Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, Kashihara, Japan

Abstract: Thyroid metastasis is rarely diagnosed, and the treatment outcomes in p16-positive oropharyngeal squamous cell carcinoma patients with rare thyroid metastasis have not been fully investigated. Here we describe the case of a patient with p16-positive oropharyngeal squamous cell carcinoma who was diagnosed with cT4 N2M1 with rare thyroid metastasis. The patient was a current smoker and was positive for human papillomavirus DNA, with disease progression at 49 days and death at 113 days after completion of cisplatin-based concurrent chemoradiotherapy. *J. Med. Invest.* 67:189-191, February, 2020

Keywords: thyroid metastasis, oropharyngeal squamous cell carcinoma, p16-positive, HPV-DNA, smoking status

INTRODUCTION

p16 was established as a surrogate immunohistochemical marker of human papillomavirus (HPV) –mediated oropharyngeal squamous cell carcinoma (OPSCC) in the eighth edition of the American Joint Committee on Cancer Staging Manual (1). Previous studies reported that patients with p16-positive OPSCC had better survival outcomes than those with p16-negative OPSCC (2-6). Metastasis of the thyroid gland is rarely diagnosed in the clinical practice; only 46 patients with rare thyroid metastasis were found in 18,105 thyroidectomies and 29,708 cytological examination over a 10-years period (9). Moreover, there were no mention of thyroid metastasis in a systematic review of the end organs of distant metastasis in 220 patients developing of HPV-positive OPSCC (3). Therefore, the treatment outcomes of p16-positive OPSCC with rare thyroid metastasis remain unclear (7). Here we report the survival outcomes of a patient with p16-positive OPSCC with rare thyroid metastasis.

CASE PRESENTATION

A 69-year-old man with a 3-year history of hoarseness and dysphagia was referred to our hospital after the previous hospital diagnosed him with pharyngeal squamous cell carcinoma based on biopsy. The patient was a 49 pack-year current smoker according to a previous report (2). The habit of alcohol consumption was once a week for 40 years. Bilateral neck lymph nodes were palpable. Inspection and endoscopy revealed that the pharyngeal tumor had spread to the left tonsil, base of the tongue, left pyriform sinus, and lingual surface of the epiglottis; bilateral recurrent nerves palsy was also noted. Enhanced/plane computed tomography (CT) performed from the cervix to the pelvis revealed an oropharyngeal tumor at the base of the tongue. The tumor had spread to the extrinsic muscle of the tongue, and the

main lesion had a maximum size of 60 mm, with bilateral neck metastasis not larger than 30 mm and heterogeneity of bilateral thyroid (Figure 1). The patient was hospitalized for narrow airway and dysphagia upon his first visit to our hospital.

After hospitalization, p16 immunohistochemistry (CINtec Histology Kit, clone E6H4, Ventana, Tucson, AZ, USA) of the oropharyngeal tumor was performed using an automatic machine (Ventana BenchMark XT), which indicated that the tumor had diffused and was strongly positive. Echo-guided cytology of the bilateral thyroid indicated metastatic squamous cell carcinoma (Figure 2). Thus, p16-positive OPSCC of cT4N2M1 with rare thyroid metastasis was diagnosed based on the 8th edition of the American Joint Committee on Cancer Staging Manual (1).

Cisplatin-based concurrent chemoradiotherapy (CRT) for organ preservation definitively underwent after gastrostomy

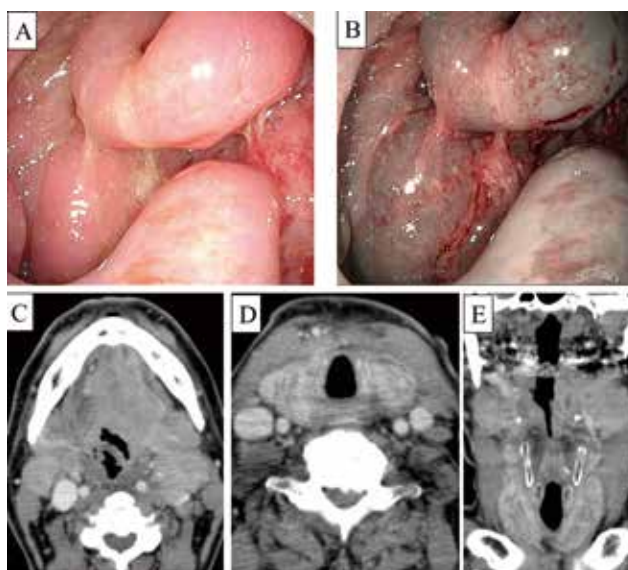


Figure 1. (A) White light and (B) narrow-band endoscopy images as well as (C) axial oropharyngeal, (D) axial thyroid, and (E) coronal thyroid enhanced computed tomography images in oropharyngeal cancer.

Received for publication May 20, 2019; accepted August 9, 2019.

Address correspondence and reprint requests to Hidenori Suzuki, Department of Head and Neck Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan and Fax: +81-52-764-2963.

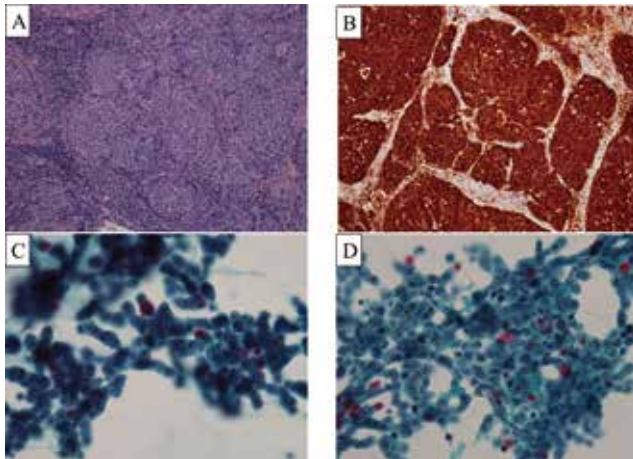


Figure 2. (A) Hematoxylin and eosin staining as well as (B) p16 immunohistochemical sections for oropharyngeal tumor and (C) right and (D) left Papanicolaou staining sections of the thyroid.

and tracheostomy for hypoxemia. A total of 70 Gy with 2 Gy/daily fraction was performed by intensity-modulated radiotherapy (RT) following three-dimensional conformal RT to the whole neck. Cisplatin (one cycle of 100mg/m²) was administered triweekly to the patient; however, the dosage was reduced to two to three cycles of 80 mg/m² because of febrile neutropenia. The first hospitalization period lasted 75 days.

At 49 days following the completion of CRT, enhanced CT revealed tumor reduction in the RT field as well as multiple distant lymph node metastases affecting the mediastinum, hilum, and axilla in areas other than the RT field. Additionally, echo-guided cytology of the axillary lymph node revealed metastatic squamous cell carcinoma (Figure 3). The patient was diagnosed with disease progression due to multiple distant metastases, and the best supportive care was selected owing to general fatigue. The patient was subsequently re-hospitalized because of dyspnea due to pleural effusion and carcinomatous carcinomatosa, and eventually died. The re-hospitalization period lasted 7 days. The durations from pathological diagnosis and completion of CRT to death were 197 days and 113 days, respectively. HPV DNA-positive was detected in formalin-fixed, paraffin-embedded tumor specimen by HPV testing using GP5+/GP6+ PCR, according to a previous report (8). HPV 16 was identified based on the L1 sequence (Figure 4).

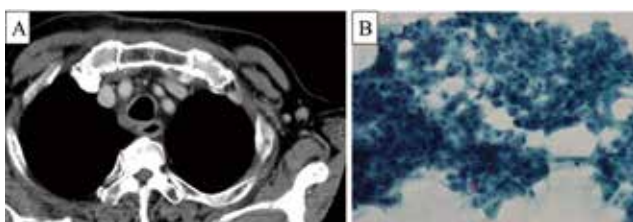


Figure 3. (A) Axial enhanced computed tomography image and (B) Papanicolaou staining of the axillary lymph node.

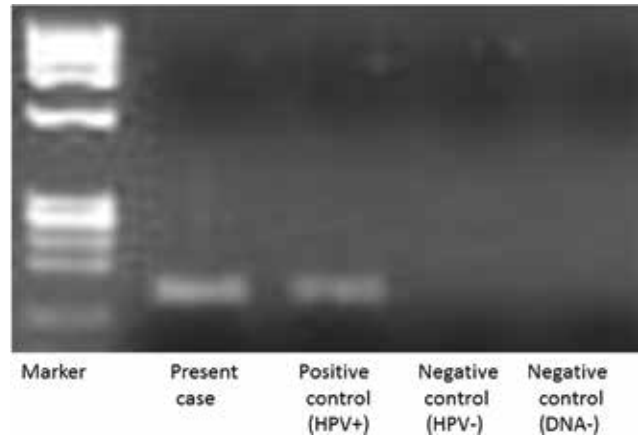


Figure 4. Polymerase chain reaction gel migration of GP5+/GP6+ primers from the oropharyngeal tumor.

DISCUSSION

Rare thyroid metastasis, accounting for 0.13% of all thyroidectomies (9), has been reported as a case report in various tumors such as neuroendocrine tumor from our hospital (10). Thyroid metastasis of p16-positive OPSCC is rare and has unknown survival outcomes (7). A recent systemic review of 453 articles, including 220 cases developing distant metastasis of OPSCC with HPV, revealed that the end organs of distant metastasis were the lung (160/220), bone (39/220), and non-regional lymph nodes (34/220); however, no rare thyroid metastasis was reported (3). Moreover, the survival outcomes of two cases with thyroid metastasis among 80 cases with recurrent p16-positive OPSCC were unclear (4).

Among patients without distant metastasis, those with p16-positive OPSCC had better outcomes than those with p16-negative OPSCC (2-4, 6). Moreover, among patients with distant metastasis, those with p16-positive OPSCC (28% at 1-year) had significantly better post-distant metastasis survival rate than those with p16-negative OPSCC (13% at 1-year) (5). As a clinical predictor in patients with p16-positive OPSCC, those with current smoker showed worse outcomes than those with never smoking history (2, 6). A large cohort study demonstrated in 2018 that 48 patients with p16-positive OPSCC who were negative for HPV DNA had significantly shorter survival outcomes than 340 patients who were positive for HPV DNA and had similar survival outcomes as 816 patients with p16-negative OPSCC (12).

Considering the clinical stage and treatment strategy in a recent and similar case with a favorable course of p16-positive OPSCC with rare thyroid metastasis that did not assess HPV DNA and smoking status, no tumor recurrence observed 6 months after total thyroidectomy following definitive CRT (7). In contrast to the previous report (7), our patient presented an unfavorable course in terms of disease progression at 49 days and death at 113 days following definitive CRT. Because p16 positivity was a surrogate marker of HPV (11), the present case was examined for p16-positive OPSCC with HPV-negative DNA. Although the HPV DNA status was not reported in the previous case (7), the present case was both p16 and HPV DNA positive. Our study suggests the patient's current smoking status possibly led to the unfavorable outcome. We believe that this patient's poor prognosis was strongly affected by his current smoking status, which has been independently indicated as a poor predictor for OPSCC in a randomized trial (6). Further accumulation

of cases of p16-positive OPSCC with rare thyroid metastasis, including smoking status and HPV DNA, is required. Although alcohol consumption has been reported to negatively influence survival (1), we were unable to suggest the role of alcohol consumption in the development and progression of the cancer in this patient.

CONCLUSION

We report that case of a patient with p16-positive OPSCC with rare thyroid metastasis and current smoking status who was positive for HPV DNA. The patient exhibited disease progression at 49 days and died 113 days after CRT.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Yutaro Koide for stimulating discussion and patient's care.

REFERENCES

1. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR : AJCC Cancer Staging Manual, 2016 8th edition. Springer ; New York.
2. Vawda N, Banerjee RN, Debenham BJ : Impact of smoking outcomes of HPV-related oropharyngeal cancer treated with primary radiation or surgery. *Int J Radiat Oncol Biol Phys* 103(5) : 1125-1131, 2019
3. Tiedemann D, Jakobsen KK, von Buchwald C, Grønhoj C : Systematic review on location and timing of distant progression in human papillomavirus-positive and human papillomavirus-negative oropharyngeal squamous cell carcinomas. *Head Neck* 41(3) : 793-798, 2019
4. Guo T, Qualliotine JR, Ha PK, Califano JA, Kim Y, Saunders JR, Blanco RG, D'Souza G, Zhang Z, Chung CH, Kiess A, Gourin CG, Koch W, Richmon JD, Agrawal N, Eisele DW, Fakhry C : Surgical salvage improves overall survival for patients with HPV-positive and HPV-negative recurrent locoregional and distant metastatic oropharyngeal cancer. *Cancer* 121(12) : 1977-1984, 2015
5. Huang SH, Perez-Ordóñez B, Weinreb I, Hope A, Massey C, Waldron JN, Kim J, Bayley AJ, Cumming B, Cho BC, Ringash J, Dawson LA, Siu LL, Chen E, Irish J, Gullane P, Hui A, Liu FF, Shen X, Xu W, O'Sullivan B : Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral Oncol* 49(1) : 79-85, 2013
6. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML : Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 363(1) : 24-35, 2010
7. Takenobu M, Moritani S, Yoshioka K, Morisaki T, Kitano H : A case report of thyroid metastasis from p16-positive oropharyngeal squamous cell carcinoma. *Endocr J* 65(4) : 479-483, 2018
8. Cannavo I, Loubatier C, Chevallier A, Giordanengo V : Improvement of DNA extraction for human papillomavirus genotyping from formalin-fixed paraffin-embedded tissues. *Biores Open Access* 1(6) : 333-7, 2012
9. Papi G, Fadda G, Corsello SM, Corrado S, Rossi ED, Radighieri E, Miraglia A, Carani C, Pontecorvi A : Metastases to the thyroid gland : prevalence, clinicopathological aspects and prognosis : a 10-year experience. *Clin Endocrinol (Oxf)* 66(4) : 565-571, 2007
10. Yamada H, Hasegawa Y, Mitsudomi T, Nakashima T, Yatabe Y : Neuroendocrine tumor metastasis to the thyroid gland. *Int J Clin Oncol* 12(1) : 63-67, 2007
11. Smeets SJ, Hesselink AT, Speel EJ, Haesevoets A, Snijders PJ, Pawlita M, Meijer CJ, Braakhuis BJ, Leemans CR, Brakenhoff RH : A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. *Int J Cancer* 21(11) : 2465-72, 2007
12. Nauta IH, Rietbergen MM, van Bokhoven AAJD, Bloemena E, Lissenberg-Witte BI, Heideman DAM, Baatenburg de Jong RJ, Brakenhoff RH, Leemans CR : Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. *Ann Oncol* 29(5) : 1273-1279, 2018