

A case report: Epstein-Barr virus-associated undifferentiated carcinoma of the tongue base

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TITLE: “A Case Report: Epstein-Barr Virus-Associated Undifferentiated Carcinoma of the Tongue Base”

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Short title: Undifferentiated Carcinoma of the Tongue Base

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ABSTRACT

Outside the nasopharynx, undifferentiated carcinomas occur only rarely at other head and neck locations. Although the association between undifferentiated nasopharyngeal carcinoma and Epstein-Barr virus (EBV) is consistent, there is conflicting evidence as to the association of EBV with undifferentiated carcinomas outside the nasopharynx. Here, we report on a case of undifferentiated carcinoma of the tongue base.

A 71-year-old male, who had been treated with irradiation for primary unknown right neck metastatic EBV-positive undifferentiated carcinoma nine years previously, was referred to our clinic with masses at the tongue base and right neck. The lesion at the tongue base was revealed to be an EBV-positive undifferentiated carcinoma. He was treated with resection of tongue base tumor and bilateral-neck dissection, and the defect at the tongue base was reconstructed with a free rectus abdominis myocutaneous flap. Re-irradiation was added post-operatively because of a positive surgical margin at the tongue base. The patient is presently alive without recurrence or distant metastasis 20 months after treatment.

Although it is unclear whether our case is recurrent or newly developed EBV-latently infected undifferentiated carcinoma, we propose that EBV-associated tumors should be carefully observed after treatment at least for more than ten years.

KEY WORDS: Undifferentiated carcinoma. Oropharynx. Epstein-Barr virus (EBV).

Epstein-Barr virus-encoded small RNAs (EBERs)

INTRODUCTION

The consistent association of undifferentiated nasopharyngeal carcinoma with Epstein-Barr virus (EBV) has been based on serologic and immunologic data, as well as on the demonstration of viral antigens and viral DNA and/or RNA in the respective tumor cells [1]. Outside the nasopharynx, undifferentiated carcinomas occur only rarely at other head and neck locations, including the oropharynx, laryngo-hypopharynx and salivary gland [2, 3, 4, 5, 6]. Although morphologically similar, there is conflicting evidence as to the association of EBV with oropharyngeal undifferentiated carcinomas [7, 8].

We describe the clinicopathological features of a case of undifferentiated carcinoma at the base of tongue with neck metastasis. Involvement of EBV in this case was demonstrated using *in situ* hybridization for EBV-encoded small RNAs (EBERs).

CASE REPORT

A 62-year-old male visited a previous clinic in December 1994 with a two-month history of a right neck mass. Physical examination on presentation revealed a fixed mass 3-cm in diameter at level III of the right neck. Direct laryngopharyngoscopy yielded unremarkable findings. The cervical lesion was biopsied and histological examination revealed metastatic EBERs-positive undifferentiated carcinoma (Fig.1A, B). Although the analysis of antibodies to the EBV capsid antigen (VCA) also revealed elevations of the Ig G and Ig A titers to 1:640 and 1:20, respectively, (normal is less than 10, respectively), a biopsy from the nasopharynx didn't show any malignant histology. Galium scanning did not show any potential pathological uptake indicating a primary tumor. The patient was treated with radiotherapy. The right side of the neck and the oropharynx received a total of 60 Gy, given at a dosage of 2 Gy daily. The nasopharynx was not involved in the irradiation field. Radical radiotherapy produced a good response, and the patient had shown no evidence of residual or recurrent disease for nine years. However, during follow-up, magnetic resonance imaging (MRI) revealed a tumor at the right side of the tongue base (Fig. 2A) and also the enlargement of a

lymph node at level IV of the right neck (Fig. 2B). Whole-body 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) exhibited a strongly positive 18F-FDG uptake in the right level IV lymph node and the right side of the base of the tongue, and also a weak uptake in the left cervical lymph nodes (Fig. 2C).

The patient was referred to our clinic (Fig. 3). VCA-Ig G and Ig A titers were 1:160 and 1:20, respectively. The lesion at the tongue base was biopsied and histological examination revealed EBERS-positive undifferentiated carcinoma (Fig. 4A, B). The patient was surgically treated with resection of the tongue base tumor and bilateral neck dissection, and the defect at the tongue base was reconstructed with a free rectus abdominis myocutaneous flap. Histopathological examination revealed a positive surgical margin at the tongue base, and lymph nodes with metastatic carcinoma only at level IV of the right neck. Re-irradiation for the tongue base (20 Gy) and whole neck (40 Gy) was added post-operatively. After the completion of treatment, VCA-Ig G and Ig A titers were 1:160 and <1:10, respectively. The patient is presently alive without recurrence or distant metastasis 20 months after treatment (Fig. 5A, B).

DISCUSSION

Although undifferentiated carcinomas are common in the nasopharynx, reports of occurrences in the tonsil and tongue base are rare. Undifferentiated carcinomas have the same morphology as undifferentiated nasopharyngeal carcinomas, but their association with EBV appears to be influenced by the location of the tumor and geographical origin of the patients [9]. Although nineteen cases of undifferentiated carcinoma have been reported from the tonsil, base of the tongue, uvula, soft palate, and elsewhere in the oral cavity, the association of EBV with the development of oropharyngeal undifferentiated carcinomas has not been well elucidated [8]. However, our case was revealed to be EBV-positive because EBERs were clearly detected in the nucleus of tumor cells. Furthermore, after surgical resection of the tumor, the VCA-Ig A titer was decreased to an undetectable level. Although we need to collect evidence from a number of cases to show the possibility of the involvement of EBV in the pathogenesis of oropharyngeal undifferentiated carcinomas, this evidence indicates that EBV is involved in the pathogenesis of undifferentiated carcinomas in at least some oropharyngeal undifferentiated carcinoma cases.

Maeda *et al.* reported that there was no case of oral squamous cell carcinoma (SCC) with poor differentiation in the EBV-negative group. EBV-DNA was detected in all six cases of poorly differentiated oral SCCs [10]. These results suggest that EBV-DNA replicates may be associated with the poor differentiation of squamous cell epithelium. However, Kobayashi *et al.* detected EBV-DNA in 7 out of 46 oral SCCs, and all seven positive samples were well-differentiated carcinoma, which suggested a possible relationship between EBV infection and well-differentiated carcinoma tissue [11]. Thus, it is not yet evident whether oropharyngeal carcinomas, especially at the level of differentiation, are EBV-associated.

Shimakage *et al.* reported that the incidence and intensity of fluorescence reacted on these EBV proteins were extremely high in samples from cases with poor prognosis, such as early recurrence, and that metastases exist according to the increase of EB viral protein synthesis [12]. However, Maeda *et al.* stated that EBV infection is not related to tumor response to radiotherapy, or the prognoses of the patients [10]. Horiuchi *et al.* also showed no correlation between the presence of EBV and the T-category, the incidence of lymph node metastasis, or the complete remission rate. There was also no

significant difference between the EBV-positive and EBV-negative patients with respect to their 5-year survival rates [10, 11]. Thus, the association between EBV and prognosis for these cancers remains unclear.

It seems reasonable to suppose that our case is a newly developed undifferentiated carcinoma at the tongue base, because nine years has passed since the primary therapy with irradiation. However, from the literature, the 10-year actuarial rate of mucosal carcinoma emergence is from 14 to 20 % after radiotherapy for patients with primary unknown cervical metastasis [13, 14]. In addition, metastatic lymph nodes were detected only at level IV of the right neck, which is not a physiological pattern of lymphatic spread of a newly developed tongue base carcinoma. Thus, it is also possible that our case is a recurrent tumor that emerged at the tongue base nine years after the initial treatment. Although a method to distinguish between a newly developed tumor and a recurrent tumor has not been established, checking the number of terminal repeats of a latently infected EBV genome should be a method of choice to determine the differences in the clonality of the EBV-positive tumor cells. Finally, we propose that EBV-associated tumors, including NPC, should be carefully followed up for longer

period, at least for more than ten years.

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FIGURE LEGENDS

Fig. 1. A. Hematoxylin & eosin (HE) staining (original magnification x 200). Metastatic undifferentiated carcinoma of the right cervical lymphnode. The neoplastic cells are large-sized, with vesicular nucleoli, and indistinct cytoplasmic borders. B. RNA *in situ* hybridization using an EBERS probe, counter stained with methylgreen (original magnification x 200). Positive signals are seen in the nuclei of almost all of the cancer cells.

Fig. 2. A. An axial gadolinium enhanced T1-weighted MRI image showing a homgenously enhanced ulcerated mass involving the right side and beyond the midline of the tongue base (Arrow). B. A coronal gadolinium enhanced T1-weighted MRI image demonstrates an enlargement of the right level IV lymph node (Arrow). C. Positive focal uptake in the tongue base and the right level IV lymph node on PET. Weak uptakes in the left cervical lymph nodes were also exhibited.

Fig. 3. Endoscopic view of the tumor of the tongue base before treatment (Arrowheads

demonstrate the extent of the tumor). The surface of the lesion is ulcerative. Biopsy of the lesion revealed undifferentiated carcinoma. Arrow: epiglottis.

Fig. 4. A. HE staining (original magnification x 200). Undifferentiated carcinoma of the tongue base showing the proliferation of tumor cells with marked lymphocyte infiltrates. The tumor cells are medium sized, with prominent nucleoli, and indistinct cytoplasmic borders. B. RNA *in situ* hybridization using an EBERs probe, not counter stained (original magnification x 200). Positive signals are seen in the nuclei of almost all of the cancer cells.

Fig. 5. A. Postoperative endoscopic view of the oropharynx. Arrowheads indicate the free rectus abdominis myocutaneous flap, which fills the defect after surgical resection of the tumor of the tongue base. Arrow: uvula. B. Postoperative CT at 20 months after surgery. Arrowheads demonstrate the extent of the myocutaneous flap. The patient is currently alive without locoregional recurrence or distant metastasis.