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CASE REPORT

Invasion of the Hypoglossal Nerve by Adenoid Cystic Carcinoma of the Tongue: Case Report and Review of the Literature

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Abstract Adenoid cystic carcinoma (ACC) is a rare but highly aggressive malignancy mainly originating from the salivary glands. ACC is well known for its propensity toward neural invasion (NI). NI is the process of neoplastic invasion in and along nerves. It is a distinct and well-documented phenomenon in ACC; however, it is an underestimated route of metastatic spread. Multiple distant metastases can be established through NI route, and NI is believed to portend a poor prognosis. Despite increasing recognition of NI in many malignancies, the molecular mechanism behind NI is not well established. We present a unique case of hypoglossal nerve invasion by ACC arising from the minor salivary glands in the tongue of a 34-year-old man. We also review and discuss current theories on the pathogenesis and mechanism of NI.

Keywords Neural invasion · Adenoid cystic carcinoma · Hypoglossal nerve · Tongue · Treatment

Introduction

Adenoid cystic carcinoma (ACC) comprises approximately 7.5–10% of all salivary malignancies and 1% of all head and neck malignancies [1, 2]. Conspicuous clinical features of ACC include slow growth, neural invasion (NI), local recurrence, and distant metastasis. Although influence of NI on survival has been contradictory [2], it is widely accepted that neurotropism and spread by neural invasion may be reasonable explanations for its propensity for local recurrence and distant metastasis, owing to unexpected extension beyond apparently clear resection margins [3]. To our knowledge, only 1 case of hypoglossal nerve invasion by ACC has been reported till date [4]. In this article, we report an additional case of such involvement by extensive ACC arising from the minor salivary glands in the tongue of a 34-year-old man who was treated with surgery and adjuvant radiotherapy. We also carried out a brief review of the literature and discussed current theories on the pathogenesis and mechanism of NI.

Case Report

In December 2008, a 34-year-old Chinese man was admitted to the Department of Head and Neck Surgery of Sun Yat-sen University Cancer Center. The patient first felt pain on the right side of his tongue in June 2005. The pain gradually worsened over the next half year. He noticed a slight swelling of the tongue in December 2005. The pain and swelling continued to aggravate until December 2006, when he began to develop difficulty in moving the right side of his tongue. Over the last 9 months, he experienced problems with speech and mastication.

Shu-Wei Chen and Zhu-Ming Guo contributed equally to this work.

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Oral examination indicated that the patient had limited lingual movement. The right side of the tongue was found to be swollen, firm, and indurated, but with normal looking mucosa. A lymph node was present in the right level IIA of the neck measuring about 20×15 mm, which was stiff and mobile with a clear border.

An enhanced magnetic resonance imaging (MRI) scan of the oromaxillofacial region and neck was performed, which indicated an irregular-shaped mass in the right side of the tongue measuring 50×54×46 mm (Fig. 1a) that extended to infiltrate the floor of the mouth. The lesion invaded the right lateral wall of the oropharynx and the preepiglottic space. Furthermore, MRI showed 3 enlarged lymph nodes in the ipsilateral neck: 1 (32×18 mm) at level IIA (Fig. 1b) and 2 (9.5×8.5 mm and 8.5×5.5 mm) at level III (Fig. 1c and d), which were diagnosed as metastatic disease. A core needle biopsy of the mass was performed under local anesthesia. The specimen revealed a minor salivary gland tumor beneath the covering mucosa, the histopathologic appearance being consistent with that of an adenoid cystic carcinoma. The chest radiograph was normal.

The patient underwent a subtotal glossectomy and total resection of the floor of mouth and the right lateral wall of the oropharynx, along with an ipsilateral modified radical neck dissection and oral reconstruction using a trapezius myocutaneous flap. The neck specimen was removed in continuity with the primary tumor using a pull-through approach. During the neck dissection, we found that a segment of the right hypoglossal nerve, which passes deep to the posterior belly of the digastric and stylohyoid muscles, was enlarged, measuring 20×10×6 mm (Fig. 2). In view of ACC's high propensity for NI, we decided that the hypoglossal nerve was invaded by the primary lesion. The nerve was resected with a tumor-free resection margin proved by the intraoperative frozen section. The pathologic examination of the paraffin section of the specimen confirmed our presumption (Fig. 3). Three lymph nodes on the ipsilateral neck proved to be metastatic (level IIA, one node; level III, two nodes), as suggested by preoperative MRI. The patient received radiation therapy 2 months after surgery. The combined-modality treatment was tolerated well.

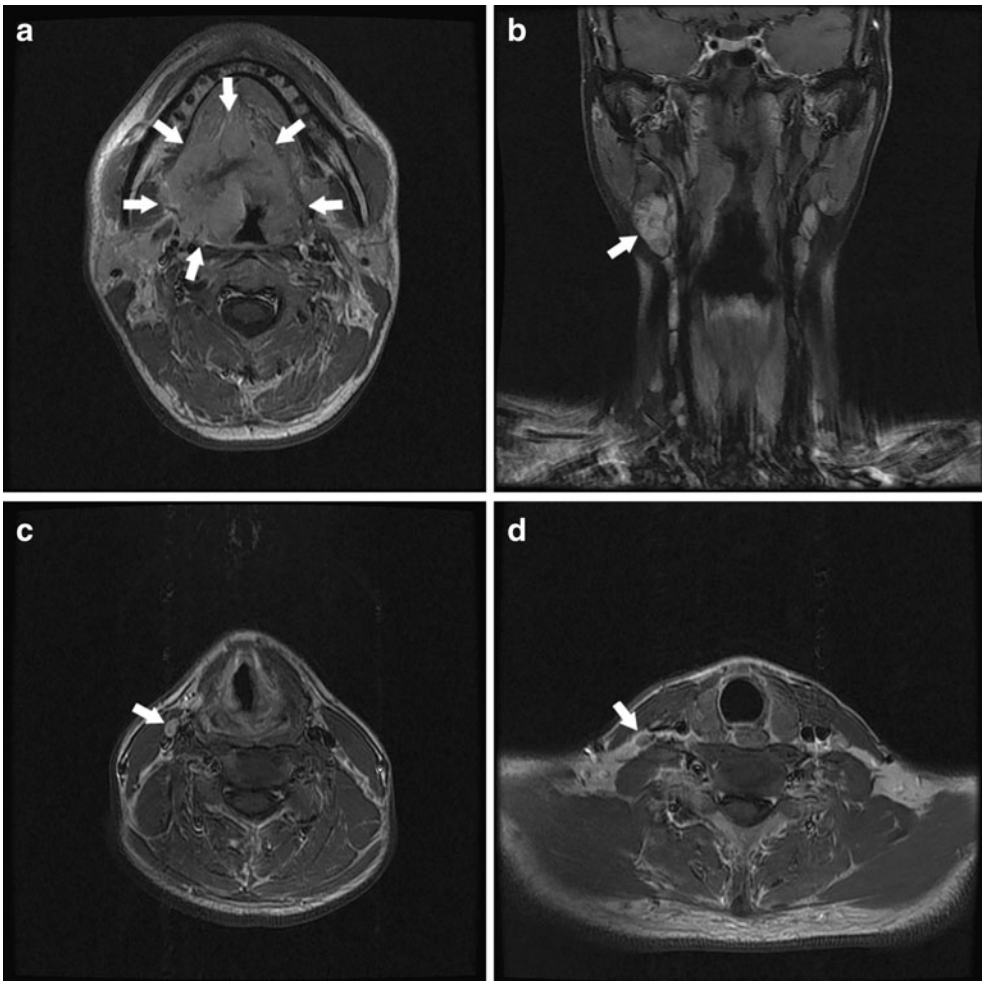

Fig. 1 Images of T1-weighted magnetic resonance imaging (MRI) by using gadolinium. **a** Tumor infiltrating to the floor of the mouth and the right lateral wall of the oropharynx, as well as the preepiglottic space. **b** Metastatic node at level IIA. **c** and **d** Metastatic nodes at level III

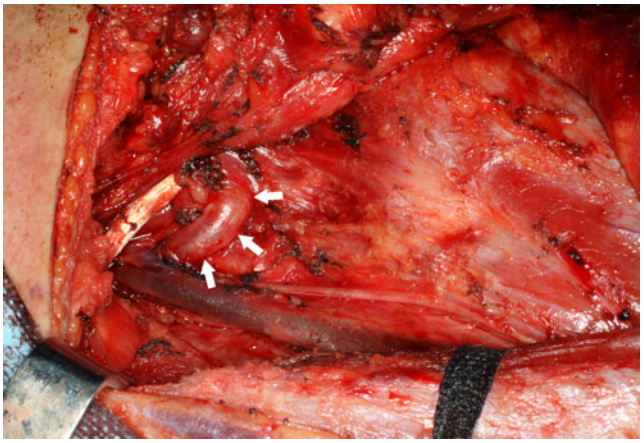

Fig. 2 Intraoperative photograph showing an enlargement of the segment of the right hypoglossal nerve in the anterior triangle of the neck

He received a close follow-up, and there has been no evidence of recurrence to date after the combined-modality treatment.

Discussion

ACC is a rare but highly aggressive malignancy that mainly affects the major and minor salivary glands. The natural history of ACC is characterized by slow growth, high incidence of local recurrence, and distant metastasis; however, NI is the most conspicuous propensity.

When ACCs occur in the oral cavity, the tongue is an unfrequently affected site, with the palate being the most common site of involvement [5]. NI has been reported to be present in 32.4–72% of the intraoral ACC specimens [6, 7]. In fact, there is lack of a concise, universal definition for NI, and identification of NI depends on the method of evaluation. Further, the identification of NI depends largely on the diligence of the examining pathologist [8]. These lead to the wide range of the reported incidence of NI in ACC. Does the occurrence of NI affect the prognosis of ACC patients? Although the WHO conclude that "the influence of perineural invasion on survival has been contradictory" [2], most clinical series [3], however, attest to the fact that neoplastic invasion of named nerves is correlated with an increased risk of local recurrence after combined surgical and radiotherapeutical treatment and subsequently a poorer prognosis.

Invasion and metastasis are key components of cancer progression. Cancer cells are capable of dissociating from the primary tumor and disseminating via lymphatic and vascular channels, which have been well characterized and are the focus of much of the current research on tumor biology. Another distinct route of metastatic spread, NI, has been increasingly recognized in many malignancies, including those arising from the pancreas [9], colon and rectum [10], prostate [11], head and neck [12], bladder [13], biliary tract [14], etc. NI has long been observed to be associated with tumor recurrence in the aforementioned malignancies. However, it has been underestimated and receives relatively little research attention, which may partly explain the slow and little progress in the molecular mechanism behind NI and thus the targeted treatment modalities relevant to this pathologic entity.

Over the past few decades, NI has been explained by the rich innervation of the organ, and it has predominantly been presumed as an extension of lymphatic metastasis, in view of the presence of lymphatic vessels inside the epineurial layer. However, recent studies have demonstrated that lymphatic vessels do not penetrate the epineurium, which contradicts the above theory.

Current theory on the pathogenesis of NI suggests that the neurotropic malignant cells may have acquired the ability to respond to proinvasive signals within the peripheral nerve milieu and that NI is the result of an active and specific mutual signal interaction between these malignant cells and nerves [15]. This theory is based on some recently well-executed investigations. Ayala et al. [16] cocultured the mouse dorsal root ganglia (DRG) with prostate cancer cells in a Matrigel matrix and found that cancer cells migrated along the neurites toward the ganglia of origin and DRG, in turn, projected toward cancer cell colonies. Cornell et al. [17] added stromal cells to the aforementioned in vitro model and observed increased neurite outgrowth as well as cancer cell colony formation. Similar results could be observed in pancreatic cancer [18]. These findings indicate the mutual tropism and paracrine interaction between invading cancer cells and neurons in

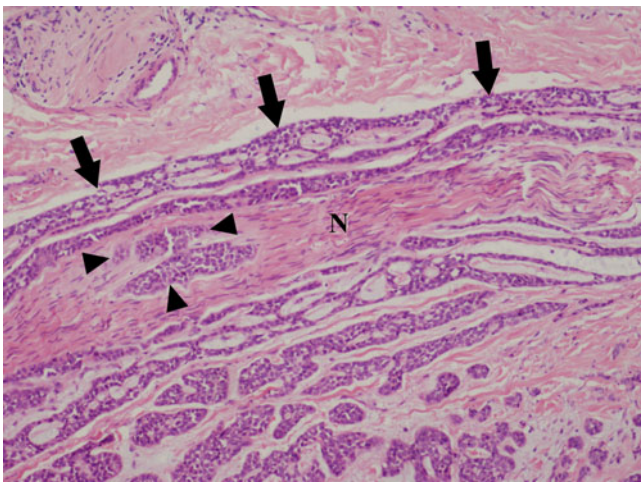

Fig. 3 Microphotograph revealing intraneural (*arrowhead*) and perineural (*arrow*) invasion of the hypoglossal nerve by a cribriform-type adenoid cystic carcinoma. Hematoxylin and eosin, original magnification 100×. N indicates the hypoglossal nerve

vitro, i.e., nerves provide a prosperous microenvironment for tumor growth and the tumor-nerve interaction benefits the growth of both the invading cancer cells and nerves. We could also conclude that the signaling mechanism behind NI involves at least three different cellular elements: nerve, cancer, and stromal cells.

Recent research on the molecular mechanisms of NI identified neurotrophic factors and chemokines as key molecular determinants in this process of metastatic spread. Ceyhan et al. [19] have found that Artemin, a member of the glial cell-derived neurotrophic factor (GDNF) family, promotes pancreatic cancer invasion of nerves as well as the growth and survival of neurotropic malignant cells. Another significant pathway in this process is the CX3CL1-CX3CR1 pathway. The chemokine CX3CL1 (also known as Fractalkine) has been demonstrated to be implicated in the ability of neurotropic malignant cells to invade peripheral nerves and establish metastatic deposits at distant sites [20].

Conclusion

We have reported a unique case of extensive ACC arising from the minor salivary glands in the tongue and briefly reviewed and discussed current theories on the pathogenesis and mechanism of NI. Better understanding of the pathogenesis and mechanism of NI and its clinical significance would help the design of innovative strategies to control tumor dissemination. As a new and profound route of metastatic spread for malignant tumors, NI will be a potential therapeutic target of malignant tumors in the near future.

Conflict of interest We declare no conflicts of interest.

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