

ORIGINAL ARTICLE

Misuse of traditional Chinese medicine may be a risk factor to tumorigenesis and progression of head and neck carcinoma in China: a hypothesis based on a case series

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Summary

Purpose: In China, many patients with head and neck carcinoma prefer traditional Chinese medicine (TCM) as their first therapy. However, several components of TCM have been identified as being toxic. We hypothesize that misuse and over-application of TCM can contribute to tumorigenesis and progression of head and neck carcinoma.

Results: Three head and neck cancer patients were the subjects of this report. The first patient with squamous cell carcinoma got TCM without surgery, chemotherapy or radiotherapy which resulted in disease progression. The patient was then subjected to palliative surgery followed by concurrent chemoradiotherapy (CCRT). The second patient with mucoepidermoid carcinoma of the parotid gland received

TMC as first-line therapy with rapid disease progression. This was followed by complete parotidectomy and postoperative CCRT. The third patient with laryngeal squamous cell carcinoma took oral TVM for 8 years to treat psoriasis. Due to recent complaints he was radically operated and received postoperative CCRT.

Conclusion: Due to its unclear components, potential toxicities, misuse, and over-application, TCM might contribute to tumorigenesis and progression of head neck carcinoma. We seek effective approaches to ensure the safe use of TCM.

Key words: traditional Chinese medicine, head and neck carcinoma, tumorigenesis, progression

Introduction

Globally, head neck carcinoma (HNC) is ranked sixth among all malignancies, with about 650,000 new diagnosed cases and 350,000 deaths per year worldwide [1]. Although some new therapies have been developed, the prognosis of this tumor type has remained unsatisfactory during recent decades [2]. Moreover, standard treatment including surgery, chemo-radiotherapy, or surgery followed by chemo-radiotherapy can significantly impair the quality of life of patients. Currently, known etiologic factors of head and neck carcinoma include tobacco smoking, alcohol consumption, high-risk HPV infection, radiation, and occupational exposure to hazardous substances [3-5].

Traditional Chinese medicine (TCM) has been utilized in China for 1000 years [6]. To date, it has been demonstrated that TCM exerts powerful effects on various diseases including allergies [7], infection [8], diabetes [9], and malignancy [10]. An increasing number of TCM agents - such as berberine [11], curcumin [12], and evodiamine [13] - have been studied for their potential use in treating cancer. In China, many patients prefer TCM to standard medicine and believe that TCM has fewer side effects [14].

Generally, TCM has its own unique principles. TCM concentrates on the balance of the whole body, such as the balance of Yin and Yang.

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Therefore, using TCM without considering this balance may lead to severe adverse effects. Nevertheless, many components of traditional Chinese herbs (TCH) have been identified as toxic. For example, aristolochine causes injury to the liver and kidney, and may even promote carcinogenesis [6].

Misuse and over-application of TCM is common in China because of gaps in safety surveillance [6,14]. In this study, we report three head and neck carcinoma patients who misused and took TCM in excess, which could have potentially caused tumorigenesis and tumor progression.

Patients' presentations

All case studies and treatment plan were approved by the institutional review board and ethics committee of the China-Japan Union Hospital of Jilin University. Informed written consent was obtained from the patients or their relatives.

Case 1: A 72-year-old female patient was referred to the Department of Otorhinolaryngology, Head and Neck Surgery of the China-Japan Union Hospital of Jilin University (Changchun, China) in October 2014. Six months earlier, she presented with a progressively enlarged unilateral mass of

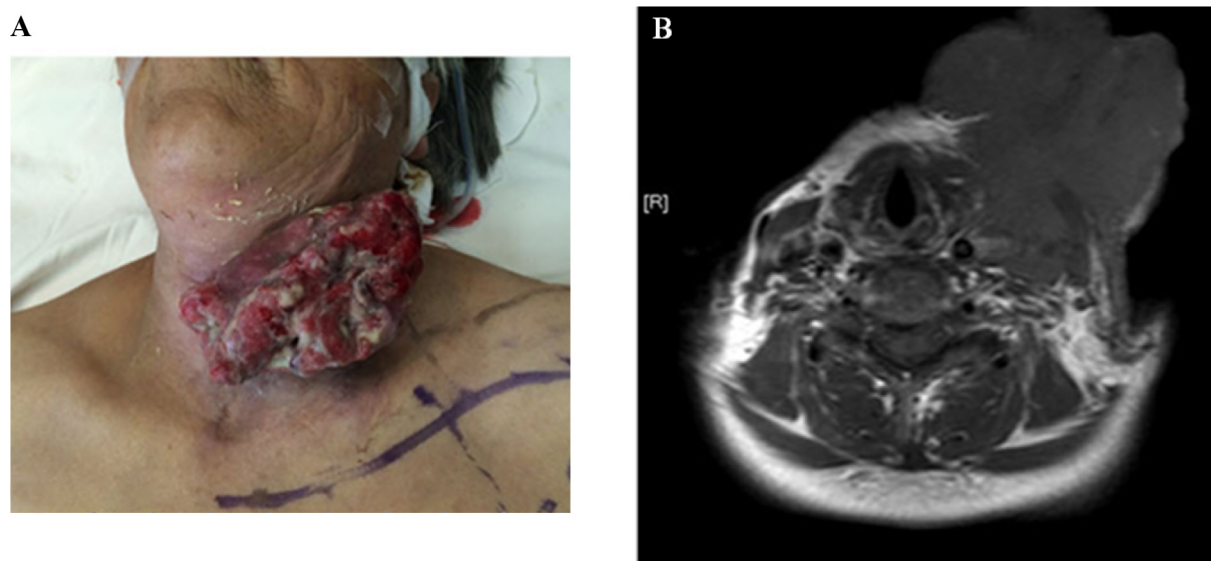


Figure 1. External and internal images of Case 1. **A:** a huge external mass on the neck. **B:** MRI scan revealing the external portion of the mass to be much larger than the internal portion.

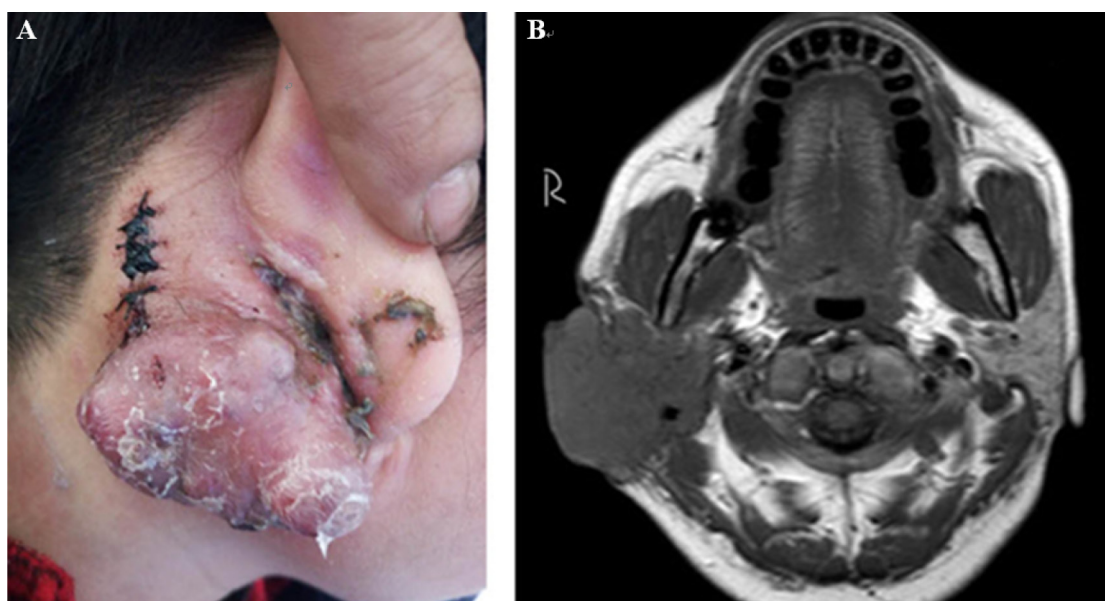


Figure 2. External and internal images of Case 2. **A:** a huge mass underneath the right ear. **B:** MRI scan revealing the external portion of the mass to be larger than the internal portion.

skin on the left side of the neck, which bled occasionally. At the beginning, she chose an unidentified TCM as a first-line treatment. Unfortunately, the initial mass enlarged progressively and erupted through the skin at the site where the TCM was applied.

A physical examination revealed a huge odorous cauliflower-like red mass located on the left side of the neck (Figure 1a). The patient had a smoking history of about 40 years. Laryngoscopy demonstrated a cauliflower-like neoplasm in the ipsilateral pyriform and pathology showed a squamous cell carcinoma. A MRI revealed an irregular mass (8.7×8.1×6.0cm) that occupied the internal side of the sternocleidomastoid muscle. The tumor also invaded the common carotid artery and grew out of the neck skin (Figure 1b). The patient received palliative surgery in our hospital and postoperative concurrent chemo-radiotherapy (CCRT) was given. She died from distant metastasis 6 months later.

Case 2: A 51-year-old woman presented with a progressively enlarged unilateral dark external mass underneath the right ear with pain that had appeared 6 months ago. When the mass first appeared, she applied an unidentified TCM as her first-choice treatment. However, her doctor misdiagnosed it as case of infection with purulent inflammation and drained out the fluid from the neck mass. Then the mass enlarged gradually and erupted from the skin larger and growing at a rate faster than the subcutaneous mass. The mass was a huge round-like dark mass with irregular edges (3×4×3cm) located on the right branchial region with a strong odor as well as pain when touched (Figure 2a).

This woman had no history of tobacco smoking or alcohol consumption. Biopsy revealed a highly

differentiated mucoepidermoid carcinoma. MRI of neck revealed that an irregular neoplasm of parotid gland invaded the sternocleidomastoid muscle as well as the extrapyramidal muscle and grew out of the neck skin. The mass had an isometric signal at T₁WI and a mixed slightly long signal at T₂WI, with an obvious inhomogeneous enhancement in contrast-enhanced T₁WI (Figure 2b). The patient underwent complete parotidectomy followed by postoperative concurrent chemo-radiotherapy (CCRT). The patient is now disease-free according to the 2-year follow-up.

Case 3: A 56-year-old male was referred to our department in May 2017. This patient had complained of dysphagia for 1 month and laryngoscopy revealed a cauliflower-like neoplasm at the epiglottis, but without invasion of the tongue root or vocal cord (Figure 3a). Preoperative biopsy indicated it was a squamous cell carcinoma.

Interestingly, this patient had no history of smoking, alcohol consumption, or occupational exposure to hazardous substances. Instead, he was taking an unaltered TCH capsule (mainly including American ginseng, *Panax notoginseng*, *Cordyceps sinensis*, dried rehmannia root, Flos Sophorae, Smilax china non L, isatis root, radix lithospermi, root-bark of peony, Herba Hedyotis and figwort) to treat psoriasis for 8 years.

Then the patient underwent a radical operation followed by CCRT. The final biopsy indicated a moderately differentiated squamous cell carcinoma (4×2.5×2cm), without invasion of the vascular system, nerves, or epiglottis cartilage. The immunohistochemistry reported EGFR (weak+), P53 (-), ki67 (40%+), P63 (+), P40 (+), and HPV16 (-) (Figure 3b). The patient was disease-free 6 months after surgery.

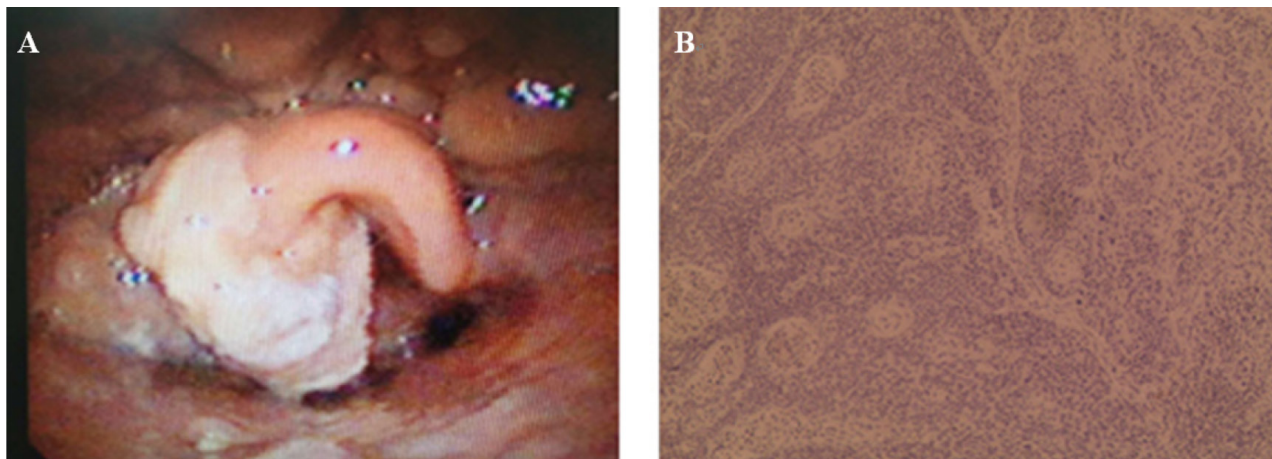


Figure 3. A: Case 3: a cauliflower-like neoplasm shown on the epiglottis. **B:** negative HPV16 expression of the tumor according to the immunohistology.

Discussion

We herein reported three cases suffering from progression of head and neck carcinoma potentially caused by TCM. To our knowledge, it is the first case series about misuse of TCM possibly causing tumorigenesis and tumor progression in head and neck cancer, however, misuse of TCM appears to be a common phenomenon in the Chinese community. We also introduced for the first time, a possible novel etiology; namely, TCM abuse causing head and neck carcinoma, and through this case series the consequences of misuse and over-application of TCM are described. The reasons that TCH may cause cancer are as follows: (1) for the first two cases, tumors exhibited special growth patterns whereby the external portion of the tumor mass grew faster and larger than the subcutaneous portion; (2) in the third case, this patient had no history of smoking, alcohol consumption, occupation exposure to hazardous substances, and radiation. A recent large case-control study supported the fact that HPV16 was mainly associated with larynx cancer in China [15]. In the present case, postoperative immunohistochemistry indicated the absence of HPV16, which suggested HPV16 infection did not participate in tumorigenesis. Of note, TCH did not contact and stimulate the larynx because this patient took capsules rather than a decoction.

The vast majority of the medical literature has focused on anticancer properties but not on toxicities of TCH. Actually, some TCH have intrinsic toxicities and even could be carcinogenic [6]. For example, aristolochic acid, a component of the family *Aristolochiaceae*, was found to induce upper tract urothelial carcinoma [16]. Although no evidence supports the intrinsic toxicities of TCH in the present report, some components such as *Radix Rehmanniae Recens*, play a similar function ("Qing Re", clear heat) with species of *Aristolochiaceae* in direction of Chinese medicine [17,18].

As previously reported, long-term medication may contribute to an imbalance, which may cause malignant transformation of epithelium [19]. Secondly, some TCH have extrinsic toxicities. Excessive amounts of heavy metals and pesticides are the most significant risk factors affecting the safe use of TCH [6].

Cordyceps sinensis was a component of TCH in the third case described above. Zuo et al. analyzed the amounts of six heavy metals including Hg, As, Cr, Cd, Cu, and Pb in natural *Cordyceps sinensis* and their related soil samples. What they found was that most As and Cu levels exceeded Chinese Pharmacopoeia standards due to the correlation with soil samples where these plants were collected [20].

Another component of TCH in our third case, *Panax notoginseng*, has been reported to be contaminated with As and Cd [6]. Consistent with our case series, some authors reported cases where TCM was associated with the development of cancer like penis squamous cell carcinoma and scalp basal cell carcinoma, respectively [21]. Therefore, long-term administration of a contaminated TCH may strongly contribute to tumorigenesis as seen our third case.

Some significant limitations in this study are the following: First, we could not identify the detailed components of the TCHs taken by the first two patients as the doctors were unwilling to disclose them. Therefore, we could not find the cause by which TCH induced carcinoma progression.

Second, there was no direct molecular evidence about the correlations between TCH and head neck carcinoma. Nevertheless, the available clinical data as well as similar cases reported by other authors strongly support the fact that TCH play major roles in tumorigenesis after excluding other risk factors in the etiology.

Third, we did not analyze non-HPV16 types in the third patient. However, a recent study suggested that there was no statistically significant association between non-HPV16 types and risk of larynx cancer [4].

Conclusion

Misuse of TCM can contribute to tumorigenesis and progression of head and neck carcinoma. Approaches for supervising the safety of traditional Chinese medicine should be developed.

Conflict of interests

The authors declare no conflict of interests.

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