

Synchronous double primary cancer of the lung and nasal vestibule: A case report and literature review

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Abstract. Squamous cell carcinoma (SCC) of the nasal vestibule is a rare tumor entity, and its occurrence combined with lung cancer is even rarer. Thus, several patients are often initially misdiagnosed or remain undiagnosed. This is the case report of a 55-year-old male patient who presented to our hospital with a neoplasm in the left lung. The patient was treated with left upper pulmonary lobectomy and the subsequent histopathological examination of the surgical specimen revealed a poorly differentiated SCC. On postoperative week 4, the patient presented with purulent and bloody discharge from the left nostril and was misdiagnosed with an upper jaw cyst. After another 3 weeks, the patient was re-admitted to the hospital with a mass of left nostril and nasal congestion. Tru-Cut biopsies from the nasal area and histopathological examination revealed a moderately differentiated SCC. According to the clinical presentation and the histopathological findings, the patient was diagnosed with double primary cancer of the lung and the nasal vestibule. The mass of the left nostril was significantly reduced in size with radiotherapy. To the best of our knowledge, there is no similar case previously reported in the literature. Due to the rarity of SCC of the nasal vestibule concomitant with lung cancer, we herein present this case report with a review of the relevant literature and investigation of the clinical characteristics.

Introduction

Multiple primary cancers are defined as ≥ 2 separate original cancers, simultaneously or successively occurring in the same or different organs. Double primary cancer is the most common type of multiple primary cancer and it is classified as synchronous carcinoma (SC) and metachronous

carcinoma (MC). SC is used to describe the second primary tumor when it is diagnosed simultaneously or within 6 months of the diagnosis of the first primary tumor. MC is used to describe the second cancer when it is diagnosed >6 months after the first primary cancer (1). The first double primary cancer was reported in 1889 by Billroth (2), whose standard of the diagnosis was that each tumor should have a different localization and independent histological appearance. In 1932, Warren and Gates established new criteria, which are still applied today: i) Both cancers must be definitively malignant according to the histopathological examination; ii) the cancers must be histologically different; and iii) it must be established that the second cancer is not a metastatic lesion of the first (3). The incidence of multiple primary cancers appears to have increased significantly. Approximately 10% of cancer patients develop another primary cancer within 10 years of the first surgery (4). However, double primary cancer of the lung and nasal vestibule is uncommon. We herein describe an extremely rare case of synchronous double primary cancer involving the left nasal vestibule and the left lung, with a review of the literature.

Case report

A 55-year-old man presented to the Qianfoshan Hospital on April 8, 2015, where he was diagnosed with a neoplasm of the left lung. The patient had noticed bloodstained sputum 5 years prior, which later disappeared. However, the symptom recurred 2 weeks prior to admission, with accompanying intermittent pain in the left hemithorax. The patient also reported loss of appetite and weight loss of 3 kg over the last 2 months. The patient had been a chronic smoker (40 cigarettes/day) and consumed alcohol (500 gr/day) for 20 years. On physical examination, there was no peripheral lymph node enlargement. The laboratory tests revealed a squamous cell carcinoma (SCC) antigen level of 2.1 ng/ml (normal value: <1.5 ng/ml); the other blood tests were all within the normal range. Contrast-enhanced computed tomography (CECT) examination of the thorax revealed a mass sized $\sim 5.3 \times 3.7$ cm in the upper lobe of the left lung (Fig. 1A). Other radiological examinations, including whole-body emission CT, did not reveal any evidence of distant metastasis, and a CT scan of the brain was unremarkable (Fig. 1B). The patient was treated with left upper lobectomy and mediastinal lymph

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node sampling. Following histopathological examination, the lesion was diagnosed as poorly differentiated SCC (pT3N0M0, IIb) (Fig. 1C). No lymph nodes were infiltrated. Three weeks later, the patient received one cycle of adjuvant chemotherapy with regular doses of nedaplatin (120 mg/day) and gemcitabine (1,600 mg/day).

On a regular visit after chemotherapy week 1, the patient presented with a small amount of purulent and bloody discharge from the left nostril, which was first diagnosed as an upper jaw cyst, and was treated with cefthiamidine antibiotics for two days (2g, twice per day). Three weeks later, the patient was re-admitted with bloody discharge from the left nostril, a mass in the nose and nasal congestion. The CT examination revealed a mass over the left nasal vestibule (Fig. 1D). Tru-Cut biopsies from the nasal area were performed and histopathological examination revealed a moderately differentiated SCC (pT2N0M0) (Fig. 1E). According to the history, the patient was finally diagnosed with double primary cancer of the lung and nasal vestibule. Following systemic evaluation, external-beam radiation treatment was recommended and the nasal tumor was significantly reduced after one cycle of radiotherapy.

Discussion

Lung cancer is one of the most commonly diagnosed types of cancer affected by population aging and changes in lifestyle, such as smoking and physical inactivity (5). Non-small-cell lung cancer is the leading cause of cancer-related mortality worldwide (5). The number of new cases of lung cancer diagnosed annually worldwide is ~1.5 million (6). Surgery, radiotherapy, chemotherapy and immunotherapy are the four most widely employed cancer treatments (7). However, Han *et al* reported that the 5-year survival rate remains very poor (8). Nasal vestibular carcinomas are uncommon and are typically SCCs. They display a natural history similar to that of skin cancers and their prognosis is more favorable compared with other cancers of the nasal cavity (9). Nasal vestibular carcinomas are often located in the nasal floor, the nasal dome, the medial crus of the lower lateral cartilage and the inner lining of the alar wing (lateral crus), and account for <3.8% of all nasal mucosal tumors and 1% of all malignant tumors of the head and neck (10-12). Human papillomavirus infection and smoking are considered to be risk factors (12). However, their prognosis remains better compared with that of other sinonasal malignant tumors, such as maxillary sinus and frontal sinus malignant tumor (13,14). The 5-year recurrence-free survival rates range widely between 20 and 92% (15-17).

To the best of our knowledge, cases of double primary cancer of the nasal vestibule and lung are extremely rare. Thus, a number of patients may be misdiagnosed or remain undiagnosed in the first visit, resulting in a delay in treatment. The patient in the present study was originally misdiagnosed with an upper jaw cyst. Taking into consideration the clinical symptoms, signs and the correlation of the examinations with the opinions of experts, including a thoracic surgeon, otolaryngologist and pathologist, the patient was finally diagnosed with double primary cancer of the lung and nasal vestibule: i) We were able to determine that the cancer of lung occurred earlier compared with that of the nasal vestibule and the possibility of pulmonary

metastatic tumor was ruled out, as the patient had first presented with bloodstained sputum 5 years prior and the CECT examination of the thorax revealed a large mass, whereas the CT scan of the brain was unremarkable. ii) Head and neck metastasis from lung cancer is an unusual event, particularly to the nasal vestibule. The larynx is a terminally located organ in regard to vascular and lymphatic circulation (18). Primary pulmonary cancer metastasis to the larynx is very rare through the vascular or lymphatic route, and metastasis to the nasal vestibule is even rarer. In addition, on preoperative clinical examination there was no cervical lymph node enlargement and the test results revealed no evidence of distant metastasis. iii) Although the histopathological diagnosis of both tumors was SCC, the degree of pathological differentiation (the level of malignancy) was different. Thus, metastatic carcinoma was deemed unlikely.

However, identification of the primary or metastatic nature of the nasal vestibular SCC is difficult. As there is no definitive evidence, it may be argued that a history of malignancy does not necessarily suggest that a nasal vestibular lesion is primary in nature. It is well-known among pathologists that there are currently no immunohistochemical markers for the determination of the likely site of origin of SCC, although this is feasible for adenocarcinomas in the majority of cases (19). Some related and heuristic studies have been performed in recent years. For example, Huang *et al* performed immunohistochemical staining to compare the expression profile of the epithelial-mesenchymal transition markers between a metastatic lesion of the duodenum and primary SCC of the hypopharynx (20). Therefore, the differentiation between primary and metastatic nasal vestibular SCC currently depends mainly on clinical and histological examination. The clinical and histological evidence confirmed that the second tumor of the nasal vestibule was primary in this case. Based on these results, the patient was diagnosed with double primary cancer of the lung and nasal vestibule.

The incidence of second cancers has increased (21-23). A study on data from the European Cancer Registry reported an overall incidence of double primary cancer of 6.3% (range, 0.4-12.9%) (24); Utada *et al* reported that the proportion of patients with a second primary tumor during the follow-up period was 8.1% (median, 1.8 years; mean, 4.3 years) (25). Filali *et al* reported variable proportions of double primary cancer, ranging between 6.1 and 10.5% (26). Furthermore, the risk of second primary cancer among cancer patient was higher compared with the risk of cancer in the general population (21-22,27-28). For example, among second primary cancers, 19.0% were diagnosed within 3 months after the diagnosis of the first primary cancer (25). Another study reported that cancer patients in Connecticut had a 31% higher risk of developing a subsequent cancer (28). The increased incidence is not only due to the population aging, but it may also be attributed to the advances in medical technology, particularly diagnostic techniques and cancer treatment modalities (29). The mechanism underlying the development of multiple primary cancers has not been fully elucidated; it may be related to the late effects of treatment for the first primary cancer, or risk factors common to the first and subsequent primary cancer, such as environmental and lifestyle factors, prolonged exposure to carcinogens, radiotherapy and chemotherapy,

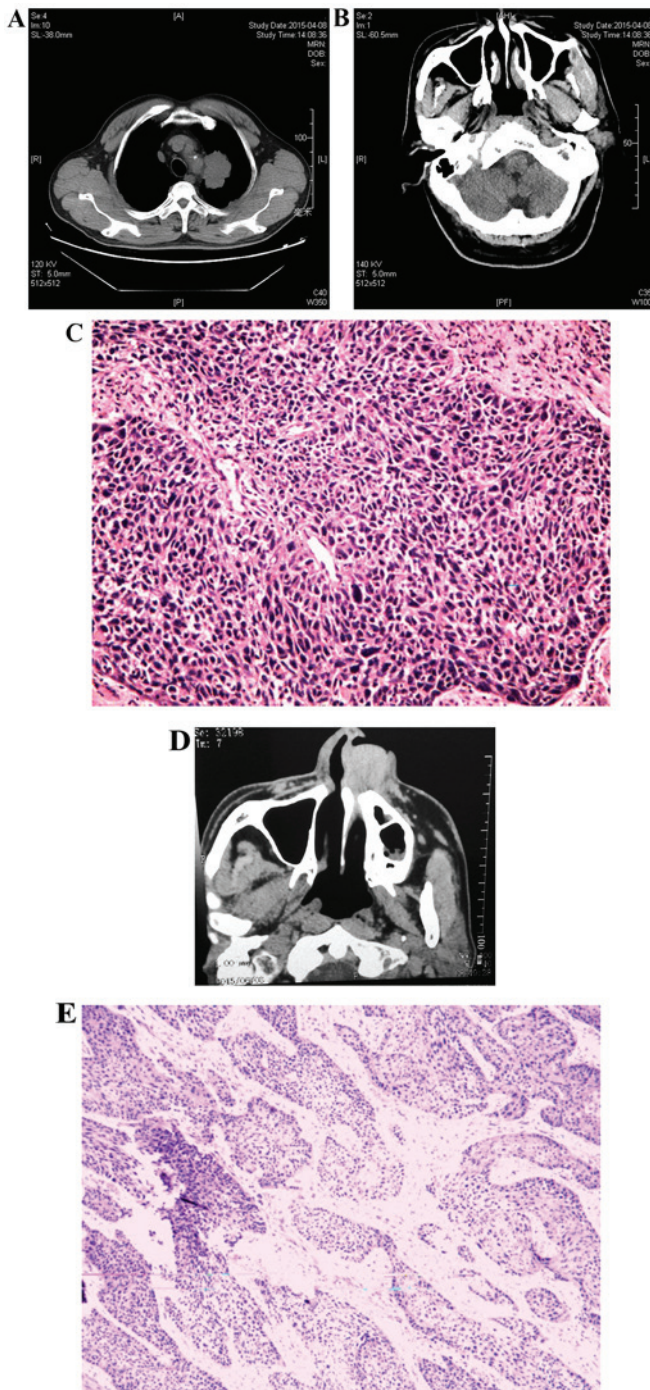


Figure 1. (A) Computed tomography (CT) scan showing a 5.3x3.7-cm mass of the left upper pulmonary lobe; (B) CT scan showing no obvious brain lesions prior to surgery; (C) the left upper pulmonary lobectomy and histopathological examination revealed a poorly differentiated squamous cell carcinoma (pT3N0M0, I1b); (D) CT scan showing a large mass of the left nasal vestibule; (E) Tru-Cut biopsies from the nasal lesion and histopathological examination revealed a moderately differentiated squamous cell carcinoma (T2).

cellular and humoral immunity deficit and individual genetic susceptibility (30-33).

Our patient underwent major invasive surgery for lung cancer. In addition, he received one cycle of adjuvant chemotherapy, which weakened the body's immune system, increasing the risk of cancer. Other important factors were the 20-year history of heavy smoking and alcohol consumption. A study reported that the major risk factor shared between first

and second primary cancers is smoking; a synergetic effect between smoking and drinking may also contribute to the development of multiple primary cancers (34-36). However, a definitive causative factor of double primary cancer has not been clearly determined; further detailed investigation on protective and risk factors is required.

For SCC of the lung, platinum-based regimens are considered as the mainstay of treatment (37). However, in our patient, although nedaplatin and gemcitabine are effective in the treatment of SCC of lung cancer, they confer no therapeutic benefit for SCC of the nasal vestibule. Wray *et al* (9) evaluated the University of Florida treatment of nasal vestibular carcinoma over a period of >40 years and reported excellent disease control with radiotherapy alone in patients with T1-T2 and favorable T3-T4. Radiotherapy and surgery result in improved likelihood of cure for patients with advanced T4 lesions. Vital *et al* (38) reported that radiotherapy is a valuable alternative treatment option avoiding potential cosmetic disadvantages. Thus, we recommend treatment with radiotherapy rather than chemotherapy for patients with SCC of the nasal vestibule. Planning to receive treatment at a local hospital, the patient was discharged. After 2 months of follow-up, the volume of the nose tumor was significantly reduced through radiotherapy and immunity-enhancing treatment.

A study in Japan reported that the esophagus, ovary, larynx, pharynx and mouth were the most frequent sites for developing a second primary cancer (21). In Queensland, Australia, from 1997 to 2001, second primary cancers of the head and neck were frequent, whereas those of the esophagus and ovary were not as common (22). However, the most common sites for occurrence second primary cancer may not be as important; all clinicians should bear in mind that, when a cancer patient is experiencing discomfort in these sites, the possibility of double or multiple primary cancers must be considered and the frequency of medical examinations and complementary tests must be increased, with the aim to improve the diagnostic rate of such patients and avoid misdiagnosis and treatment delay. Although multiple primary cancers have rarely been reported in China, their incidence is considered to be on the increase. Early detection is crucial to provide optimal treatment and improve the survival rate of cancer patients.

In conclusion, cancer patients are at a higher risk of a second primary cancers than the general population. The esophagus, ovary, and head and neck were the most frequent sites for developing a second primary cancer. Therefore, cancer patients should be under close scrutiny, particularly shortly after the diagnosis of their first primary cancer. Early detection of a silent tumor is meaningful in selecting the optimal treatment option available. Platinum-based chemotherapy is the mainstay of treatment in SCC of the lung; however, for SCC of the head and neck, treatment with radiotherapy is recommended.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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