Synchronous triple primary lung cancer of different histologies in bilateral lungs: a case report

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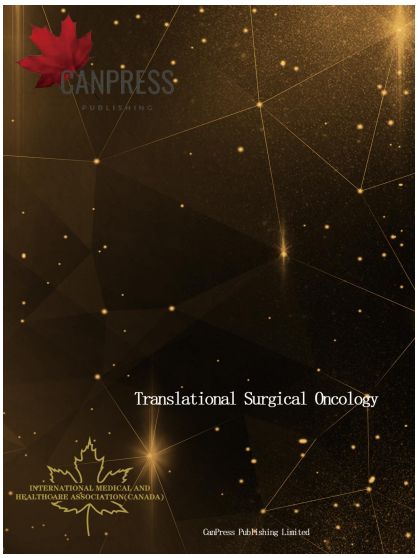

Abstract

Synchronous triple primary lung cancer is uncommon. It is a challenge to diagnose and manage synchronous triple primary lung cancer in the clinical. Here we report a rare case of 64-year-old male with synchronous triple primary lung cancer, including squamous cell carcinoma, adenocarcinoma and small cell lung cancer. Postoperative chemoradiotherapy was not effective, and the condition of the patient worsened progressively and he died seven months after surgery. The awareness of clinical and pathological characteristics of this rare disease should be increased, and effective treatment strategy needs further studies.

Keywords: synchronous triple primary lung cancer; small cell lung cancer; adenocarcinoma; squamous cell carcinoma; diagnosis and treatment

Introduction

Synchronous triple primary lung cancer (PLC) is rare in clinical practice. Only few cases have been reported[1-5]. It is easy to misdiagnose multiple pulmonary lung cancers (MPLC) as intrapulmonary metastasis, leading to the low diagnostic rate. Here we report a rare case of a 64-year-old man with synchronous triple PLC, who was treated with staged surgery but only survived 7 months after surgery because of the poor response of postoperative chemoradiotherapy.

Case report

A 64-year-old man was presented with bilateral lung lesions on chest X-ray two months ago, and he showed no symptoms. There was no abnormality in physical examination. He was a heavy smoker about 40 pack-years. Tumor markers indicated: CEA: 84.27 ng/ml, NSE: 13.69 ng/ml, Pro-Grp: 104.28 pg/ml. Chest enhanced computed tomography (CT) indicated the nodule in the left upper lobe (Fig.1 A1- A3) 2.5×2×1.5 cm, subpleural vesicular lesion in the right upper lobe (Fig.1 B1-B3) 5×2.5×1.5 cm, and the lesion in the right lower lobe (Fig.1 C1- C3) 6×4×2 cm. Examinations of bone scanning, adrenal ultrasound, and cranial CT scan were negative. Pulmonary function test indicated no abnormality. Combined with the CT features of three nodules in bilateral lungs, we considered the diagnosis of synchronous triple MPLC.

Next, we performed sublobar resection of the left upper lobe under thoracoscopy. Pathology indicated moderately-to-poorly differentiated squamous cell carcinoma (Fig.2A-D), immunohistochemistry indicated: CK7 (+), TTF-1 (+), NapsinA (-), CK5/6 (+), P63 partially (+), P40 (+), Ki-67 (30%). The postoperative recovery went well. One month later, examinarion of pulmonary function indicated no abnormality. The patient received sublobar resection of the right upper lobe and right lower lobe. Pathological examination indicated:

moderately-to-poorly differentiated invasive adenocarcinoma in the right upper lobe (Fig. 2B1-B4), including papillary type (40%), solid type (30%), acinar type (20%), micropapillary type (10%), immunohistochemistry indicated: CK7-positive, TTF-1-positive, NapsinA-positive, CK5/6 (-), P63-positive, CK20 (-), CDX-2 (-), the lesion in the right lower lobe indicated small cell lung cancer (Fig. 2C1- C4): CK7-positive, TTF-1-positive, CD56-positive, Syn-positive, CgA-positive(skin+), and focal moderately differentiated invasive adenocarcinoma (<10%) (Fig. 2D1- D4): CK7-positive, TTF-1-positive, Napsin A (-). The patient received postoperative chemoradiotherapy at local hospital, but the efficacy was poor. He suffered paralysis of lower limbs combined with urine retention three months later. The patient died of tumor progression and worse condition seven months after surgery.

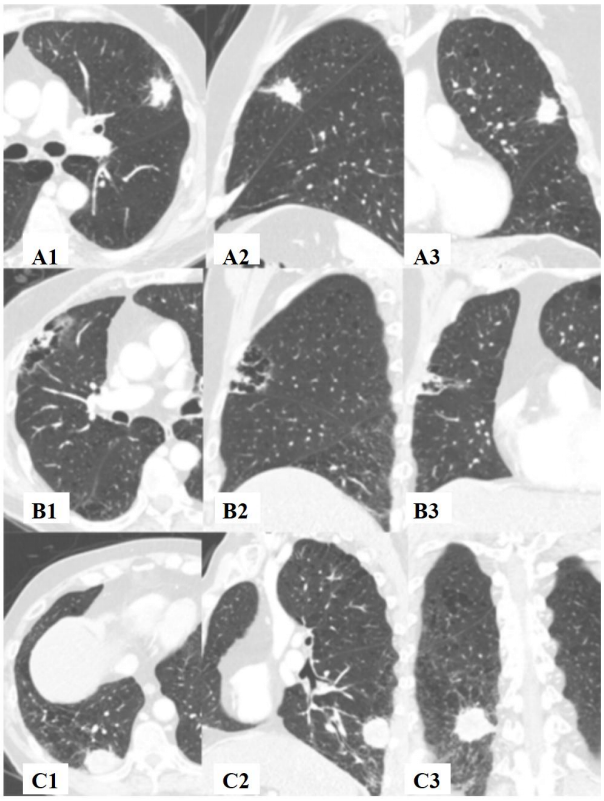

Fig.1. Imaging analysis. A1- A3: Solid density nodule with lobulation and spicule sign was seen in the upper lobe of the left lung. The enhanced scan showed uneven and obvious enhancement (A1: cross-sectional, A2: sagittal plane, A3: coronal plane), B1-B3: Nodule with multiple cystic space shadows, thick wall, consolidation and ground glass shadows was seen in the subpleural area of the upper lobe of the right lung (B1: cross-sectional, B2: sagittal plane, B3: coronal plane), C1-C3: Solid density lesion with clear lesion boundaries, visible lobules and burr was seen in the lower lobe of the right lung. Enhanced scan showed uniform mild enhancement (C1: cross-sectional, C2: sagittal plane, C3: coronal plane).

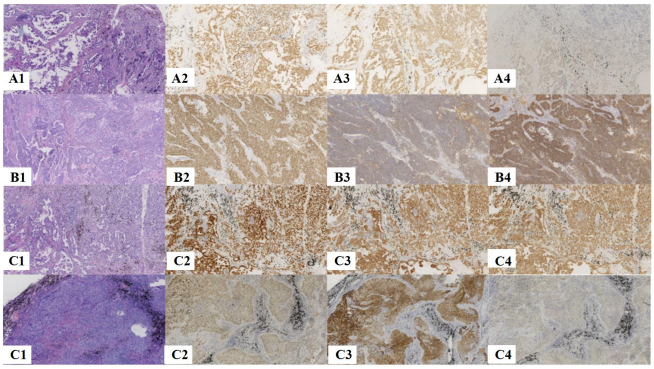

Fig. 2. Histologic and immunohistochemical analysis. A1- A4, Hematoxylin-eosin (HE) staining (A1) indicated moderately-to-poorly differentiated squamous cell carcinoma at the left upper lobe, and immunohistochemical analysis showed P63(+) (A2), CK5/6(+) (A3), CD56(-) (A4). ×100. B1- B4, HE staining (B1) indicated moderately-to-poorly differentiated invasive adenocarcinoma at right upper lobe, and immunohistochemical analysis showed TTF(+) (B2), CK7(+) (B3), CD56(-) (B4). ×100. C1- C4, HE staining (C1) indicated small cell lung cancer at the right lower lobe, and immunohistochemical analysis showed TTF(+) (C2), Syn(+) (C3), CD56(+) (C4). ×100. D1- D4, HE staining (D1) indicated moderately differentiated invasive adenocarcinoma around the lesion at the right lower lobe, and immunohistochemical analysis showed TTF(+) (D2), CK7(+) (D3), NapsinA(+) (D4). ×100.

Discussion

Simultaneous multiple primary lung cancer (sMPLC) is defined as multiple lung lesions that develop simultaneously, while metachronous multiple primary lung cancer (mMPLC) refers to multiple lung tumors that originate at different time1. The incidence of sMPLC ranges from 0.2% to 8%[6]. Synchronous triple primary lung cancers (PLCs) of different histologies is rare[1-5]. A hypothesis called field cancerization proposes that carcinogenic exposure or genetic mutation may affect tissues, inducing cells in the same area to gradually transform to atypical hyperplasia[7], so different genetic mutations and carcinogenic exposures might induce triple primary lung cancers of different lobes. According to the cases ever reported, all the patients are heavy smokers. Therefore, it is possible that heavy smoking increases the morbidity of synchronous triple MPLC. When multiple nodules are found in patients with the history of heavy smoking, the existence of MPLC might not be ignored.

Martini et al.[8] proposed the clinicopathological diagnostic criteria of MPLCs in clinical practice. Considering CT features of three nodules in bilateral lungs in our case, we made the diagnosis of synchronous triple MPLC. The postoperative pathology confirmed the diagnosis. However, it is hard to differentiate sMPLC from metastasis in clinical practice, and synchronous triple MPLC is usually found by accidence or by biospy[1-5]. Therefore, the misdiagnosis or missed diagnosis might easily occur. Interestingly, the

immunohistochemistry of the focal adenocarcinoma in the right lower lobe is same as the lesion in the right upper lobe, so intrapulmonary metastasis might be considered. The mechanism by which the tumor in the upper lobe metastasizes to the lesion in the right lower lobe is unclear and needs further studies. Tumor suppressor p53 mutation and EGFR mutation are associated with tumor pathogenesis, so they can be used to differentiate between lung metastasis and MPLC when pathological type is the same[9].

Each nodule was staged separately and surgery was performed under the principle of adequate pulmonary function preservation[4]. Staged surgery was considered preferentially with interval about one month, and the prognosis was similar to single PLC[10]. The pulmonary function of this patient was not good enough to tolerate the lobectomy. We performed staged-surgery of palliative sublobar resection of triple lesions under the principle of adequate pulmonary preservation and maximizing tumor removal. Postoperative chemoradiotherapy did not work and the patient's condition deteriorated. The patient died seven months after surgery. Kashif et al.[4] reported one case of triple PLCs with maximal diameter of 5 cm, the patient did not receive surgery due to the poor condition. After four cycles of chemotherapy with cisplatin and etoposide, the tumors did not respond to the treatment and the patient died of functional decline. These results indicate that triple PLCs might be aggressive in nature and are not sensitive to chemoradiotherapy. However, Froio et al.[1] performed left upper lobectomy and inferior apical segmentectomy with mediastinal lymphadenectomy, and the patient was alive for 27 months after chemotherapy.

According to our experience, when the lesion was too big to perform radical surgery, palliative surgery might not be considered as it might stimulate the progression of the tumor and result in potential tumor residue. Immunotherapy or immunotherapy combined with chemotherapy might be effective choice as they could improve overall survival in patients with extensive-stage lung cancer[12]. However, whether immunotherapy could be used for the treatment of triple PLCs deserves further study.

In conclusion, synchronous triple PLC of different histologies is a clinically rare disease. Increased awareness of the clinical and pathological characteristics of this rare disease can help thoracic surgeons to apply proper management. When multiple lung nodules are found simultaneously in heavy smokers, and nodules differ in the CT characteristics, the diagnosis of MPLCs should be considered.

Conflict of interest

The authors declare no conflict of interest.

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