

Post-Operative Immunohistochemical Diagnosis of Two Synchronous Primary Non-Small Cell Lung Cancers in A Single Lobe

Anand Sachithanandan, FRCSI(C-Th)*, Nor Yatizah, MPath**

*Departments of Cardiothoracic Surgery & **Pathology Serdang Hospital, Jalan Puchong, 43000 Kajang, Selangor, Malaysia.

SUMMARY

Synchronous primary non-small cell lung cancers (NSCLC) are rare and may be discovered unexpectedly following lung resection. Discrimination from intrapulmonary metastases is important to guide treatment and prognosis but is difficult solely on clinical or radiological findings. Histopathological evaluation with immunohistochemistry (IHC) markers can prove decisive and should feature in the diagnostic algorithm of such patients. We report a rare case of two synchronous primary NSCLCs diagnosed post operatively following pathological examination of the resected lobe, highlighting the value of IHC and discuss the management of such patients.

INTRODUCTION

Multiple primary non-small cell lung cancer tumours (NSCLC) are a rare occurrence and may be classified as synchronous or metachronous. Metachronous tumours are more common and by definition require a time interval between detection of the first lesion and a subsequent second primary NSCLC. Synchronous NSCLC are tumours that are detected or resected simultaneously. We report a rare case of two synchronous primary NSCLCs diagnosed post operatively following pathological examination of the resected lobe, highlighting the value of IHC and discuss the management of such patients.

CASE SUMMARY

A 69 yr old fit (*ECOG performance status 0) Chinese male smoker presented with a brief history of dyspnea but no weight loss or haemoptysis. Chest radiograph showed a right lower zone opacity and computed tomography (CT) scan revealed a solitary 5 cm spiculated right lower lobe mass with central necrosis but no mediastinal lymphadenopathy (Figure 1-A). Pre-operative radiological staging was T2a N0 M0 (Ib). CT guided biopsy confirmed an adenocarcinoma but no additional IHC was performed. Pre-operative lung function was acceptable (FEV₁ 1.39 litres 49% predicted) and the patient proceeded to surgery. A right sided bilobectomy was performed; the middle and lower lobes were resected through a 5th intercostal space posterolateral thoracotomy. Macroscopically a "golf ball" size tumour was palpable in the lower lobe however due to poorly developed fissures and associated atelectasis, the middle lobe was eventually resected concomitantly. The patient's recovery was

uneventful and he was discharged home a week later. Examination of the resected specimen revealed two separate NSCLCs in the lower lobe. The first tumour measured 30 x 23 x 32 mm within lung parenchyma with a mixed pattern predominantly papillary (> 50%) adenocarcinoma (Figure 1-C). A second tumour (40 x 31 x 65 mm) was identified 13mm away, surrounded by lung parenchyma with a mixed pattern predominantly acina (> 50%) adenocarcinoma (Figure 1-D). IHC stains for both tumours were reactive for cytokeratin (CK) -7 and thyroid transcription factor (TTF) -1 and both non-reactive for CK-20 and thyroglobulin, in keeping with two separate synchronous primary NSCLC adenocarcinomas (Figure 2).

DISCUSSION

The reported incidence of synchronous primary NSCLC ranges from 0.2-20% but appears to be increasing with advances in imaging¹. The simultaneous detection of two NSCLCs is a diagnostic challenge and has important therapeutic and prognostic implications. Two or more NSCLCs can represent synchronous lung primaries or intra-thoracic metastases from a pulmonary or extra-thoracic primary tumour. Historical diagnostic criteria for synchronous NSCLC include the presence of concurrent, separate tumours of different histology or same histology tumours arising in different locations with evidence of a carcinoma-in situ origin, non-involvement of common lymphatics or absence of extrapulmonary metastases at diagnosis². In contemporary practice, diagnosis is enhanced with IHC typing which can distinguish between a primary and metastatic NSCLC as TTF-1 and the epithelial marker CK-7 are highly sensitive and specific for a primary NSCLC and non-reactive for metastatic lung adenocarcinomas.

In this case the pathological diagnosis of two synchronous NSCLC was unexpected as the pre-operative CT revealed a solitary large tumour but no mediastinal lymphadenopathy. If more than one lesion was evident, we would have further investigated our patient with a positron emission tomography (PET) scan. Differential standardized uptake values (SUV), a measure of PET metabolic activity may help distinguish between a metastases and a second primary NSCLC as primary tumours often have a significantly higher SUV due to a higher flurodeoxyglucose (FDG) uptake. PET sensitivity for adenocarcinomas however is low due to possible false negatives and a mediastinoscopy to exclude

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Corresponding Author: A Sachithanandan, Department of Cardiothoracic Surgery, Hospital Serdang, Selangor, Malaysia

Email: anandsachithanandan@yahoo.com

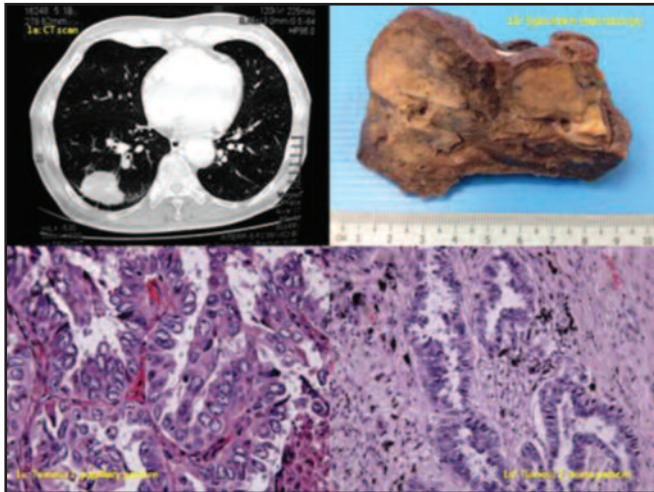


Fig. 1 : a: Computed tomogram (CT) scan demonstrating a 'solitary' spiculated large right lower lobe cancer.
b: Two distinct separate primary tumours in the right lung lower lobe separated by normal lung parenchyma.
c: Papillary histologic subtype
d: Acina histologic subtype

mediastinal N2 nodal disease might have been indicated if enlarged nodes were present despite a negative PET.

Staging of patients with synchronous NSCLC is challenging. Changes to the T (tumour) descriptor with the latest TNM nomenclature means a solitary primary tumour with ipsilateral lobe satellite nodules has been down staged from T4 to T3 and similarly, satellite nodules in a different lobe but ipsilateral lung are now classified as T4 from M1³. These changes reflect the improved survival of such patients. Long term survival following resection of synchronous NSCLCs is reportedly better than for patients with a tumour classified as stage IIIB or IV for other reasons⁵.

Despite similar histology, our patient was classified as having two synchronous primary NSCLCs for several important reasons. First, both tumours were 13 mm apart, intra-parenchymal, separate and distinct within the lobe. Second, the microscopic subhistologic pattern was different. Third and most importantly, both tumours were reactive for CK-7 and TTF-1 and non-reactive for CK-20 and thyroglobulin. Additionally, there was no mediastinal (N2) lymph node involvement on final pathological staging. CK-7 and TTF-1 positivity is highly indicative of a primary NSCLC whilst pulmonary metastases only positively stain for the CK-20 and thyroglobulin markers⁴. Limitations with CK staining include false negatives in tumours with low CK expression levels and sampling errors in a focally positive, poorly differentiated or necrotic tumour.

The optimal management of patients with synchronous NSCLCs remains controversial. Adjuvant chemo-or-radiotherapy has been advocated on the grounds of improved mid term survival following resection but is not uniformly practiced. Our patient was reluctant to attend an oncologist and furthermore, in the absence of mediastinal N2 disease and given that both synchronous NSCLCs were

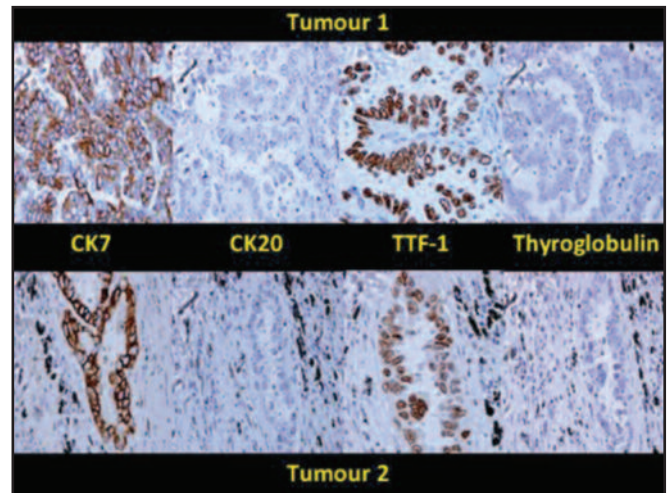


Fig. 2: IHC staining showing positivity for markers CK-7 and TTF-1 and negativity for CK-20 and thyroglobulin in both tumours in keeping with two synchronous primary lung cancers.

completely resected, no further therapy was administered. The final pathological staging was T2a N1 M0 and T2b N1 M0. Cerfolio *et al* reported similar post resection survival data for bilateral synchronous tumours regardless whether of similar or different histology. Survival was also comparable between bilateral and ipsilateral synchronous tumours⁵.

CONCLUSION

Synchronous primary NSCLCs may be an unexpected pathological diagnosis following surgery. Discrimination from intrapulmonary metastases is important to guide treatment and prognosis. Discrimination solely on clinical or radiological findings can be difficult and unreliable. Histopathological evaluation with IHC markers (CK-7, CK-20, TTF-1, thyroglobulin) can prove decisive and thus should feature in the diagnostic algorithm. For patients with a pre-operative diagnosis of synchronous NSCLC, resection should be considered in appropriately selected patients in the absence of mediastinal N2 disease due to encouraging mid term survival.

*ECOG = Eastern Cooperative Oncology Group

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