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CASE REPORT

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Transformation from lung adenocarcinoma to combined small cell carcinoma in pleural effusion after treatment with osimertinib

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combined small cell lung cancer, lung adenocarcinoma, osimertinib, pleural effusion, transformation

1 | INTRODUCTION

Lung cancer is a leading cause of cancer death worldwide with a 5-year relative survival of around 21%.[1] This poor outcome is mainly due to the late diagnosis of patients who are already at a metastatic stage. Adenocarcinoma accounts for 40% of non-small cell lung cancer (NSCLC) and a molecular profiling is recommended to set up targeted therapy when the patient is at an advanced stage. A mutation in the epidermal growth factor receptor gene (*EGFR*) leads to treatment with a tyrosine kinase inhibitor (TKI) such as osimertinib. However, acquired resistance to TKI often occurs. In this case, the most frequent mechanism is the *EGFR* secondary mutation p.T790M. Osimertinib, which is a third-generation TKI, blocks the activated *EGFR* mutant with p.T790M-resistant mutation.[2] Malignant pleural effusion is a common evolution of lung adenocarcinoma and is present in around 50% of advanced NSCLC patients. Median survival following diagnosis ranges from 3 to 12 months.[3]

We report the case of a 33 year-old woman with an acquired resistance to osimertinib, manifesting by a transformation from lung adenocarcinoma to combined small cell lung cancer (C-SCLC) diagnosed in a malignant pleural effusion.

2 | CASE REPORT

A 33-year-old woman with less than a 10 pack-year smoking history presented with haemoptysis in October 2019. Chest computed tomography (CT) showed a mass in the left lower lobe of 34 mm associated with ground glass opacities. The positron emission tomography scan confirmed a hypermetabolism of the mass, lymph node 7, and the left hilar node. A cytopuncture by endobronchial ultrasound transbronchial aspiration (EBUS-TBNA) of lymph node 7 found thyroid transcription factor 1 (TTF1)-positive carcinomatous large cells, leading to the diagnosis of lung adenocarcinoma. Molecular testing found a deletion in *TP53* and in *EFGR* exon 19. The patient first received four cures of neoadjuvant chemotherapy with cisplatin and vinorelbine. She then underwent a left lower lobar lobectomy with mediastinal lymph node dissection. The lesion measured 2.2 cm and was an infiltrative adenocarcinoma with a cribriform and solid component, without vascular invasion and with vascular rupture (of 28 nodes removed, 15 were positive among which 13 were with vascular rupture). It was classified stage pT1c pN2 M0 lung adenocarcinoma. PDL1 was not expressed. The treatment was completed with thoracic radiotherapy.

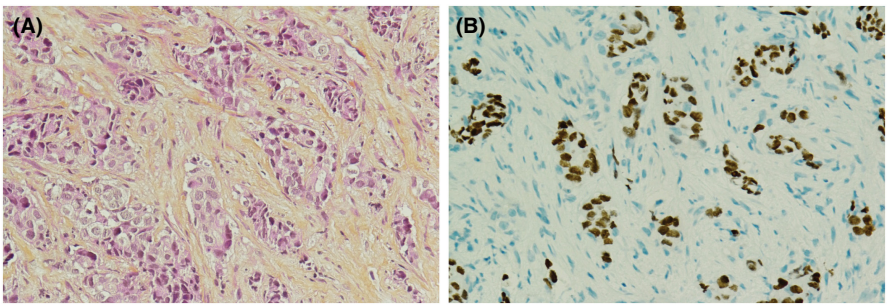

FIGURE 1 Biopsy of the left paravertebral lesion. (A) Haematoxylin and eosin staining shows an infiltrative adenocarcinoma with acinar architecture and with a fibrous stroma. (B) Immunodetection with antibody against TTF1 (clone 8G7G3/1) showing tumour cell labelling

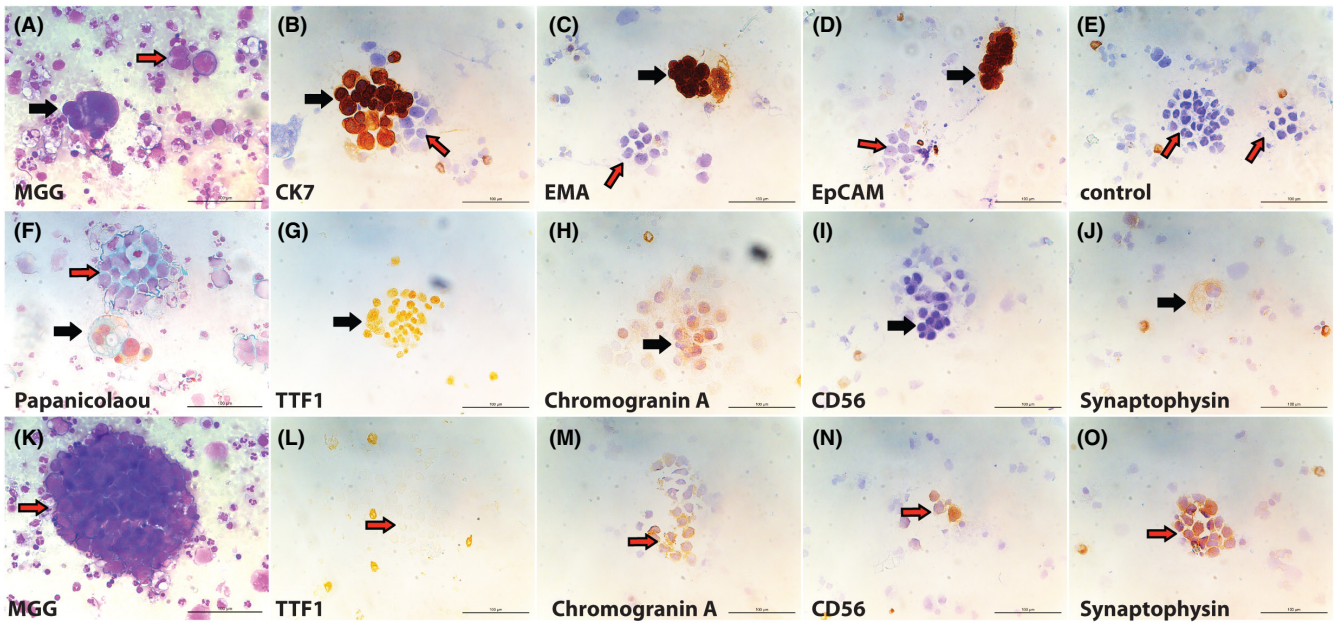

FIGURE 2 Cytology and immunocytochemistry (peroxidase staining) of pleural effusion. Briefly, fresh pleural effusion was cytospun and stained with May-Grünwald-Giemsa (MGG) and Papanicolaou. Immunocytochemistry was manually performed on frozen slides using SensiTEK HRP (scyTek) and DAB Quanto (Thermo Fisher Scientific) kits. Adenocarcinoma shows as large malignant cells positive for CK7, EMA, EpCAM, and TTF1 markers and negative for the neuroendocrine markers. Small cell lung cancer (SCLC) is seen as small cells negative for CK7, EMA, EpCAM, TTF1 markers, but positive for the neuroendocrine markers (synaptophysin, chromogranin A, and CD56 [focal staining]). (A,K) MGG. (B) CK7 (clone OV-TL12/30). (C) EMA (clone E29). (D) EpCAM (clone MOC31). (E) Mouse IgG used as isotypic control. (F) Papanicolaou. (G,L) TTF1 (clone 8G7G3/1). (H,M) chromogranin A (clone DAK-A3). (I,N) CD56 (clone 123C3). (J,O) synaptophysin (clone DAK-SYNAP). Scale bar: 100 μm. Red arrows indicate SCLC cells; black arrows indicate adenocarcinoma cells

In May 2020, the patient developed cerebral, bone, and mediastinal node metastases. Cerebral metastases (10 lesions) were treated with stereotactic radiosurgery. A treatment with the TKI osimertinib was also initiated. Follow-up 1 year later, in May 2021, showed a progression of the disease with additional bone metastases and an evolution of those already present. A left paravertebral lesion was biopsied (Figure 1) and showed an infiltrative adenocarcinoma with acinar architecture and with a fibrous stroma, confirming the diagnosis of lung adenocarcinoma metastasis. Bone lesions were treated with radiotherapy and the osimertinib treatment was continued. A new molecular testing in October 2021 on cell-free DNA found the deletion in *EFGR* exon 19 and *TP53* associated with *RB1* mutation. In November 2021, she was admitted to the emergency department with acute respiratory distress. CT revealed bilateral ground glass opacities compatible with acute respiratory distress of infectious origin in the first instance and a left pleural effusion of moderate abundance.

The pleural effusion was drained, and the cytological analysis revealed two types of malignant cells (Figure 2): a minor cell population, of intermediate size, grouped in glandular clusters, nucleated, with abundant cytoplasm; and a second major cell population, represented by clusters of smaller cells, with high nucleocytoplasmic ratio. The immunocytochemistry showed two different profiles (Figure 2). The large malignant cells were positive for cytokeratin 7 (CK7), epithelial membrane antigen (EMA), epithelial cell adhesion molecule (EpCAM), and TTF1 markers, and negative for the neuroendocrine markers in agreement with the diagnosis of lung adenocarcinoma metastasis. The small cells were negative for CK7, EMA, EpCAM, and TTF1 markers, but positive for the neuroendocrine markers (synaptophysin, chromogranin A, and CD56 [focal staining]) in favour of a SCLC profile.

The patient died several days after her admission to the hospital, preventing the confirmation by biopsy of the transformation from lung adenocarcinoma to combined small cell lung carcinoma.

3 | DISCUSSION

Histological transformation to SCLC from NSCLC has been reported as a mechanism of acquired resistance to *EGFR* TKI in 3%-15% of patients. However, the exact process that leads to this transformation remains unknown. Two hypotheses exist. The first is that the two subtypes have a common cellular origin, and that the morphological transformation occurs after TKI treatment. The second is the presence of intratumoural heterogeneity at the time of diagnosis, with a minor cell population that was not identified.[4,5] For the current patient, the whole tumour was removed at the diagnosis, and bone metastasis biopsy confirmed the diagnosis of lung adenocarcinoma. Assessments of neuroendocrine markers were retrospectively performed on the tumour and bone metastasis and were negative for both. Therefore it is unlikely that neuroendocrine cells were present but not identified. The two malignant cell populations (SCLC and adenocarcinoma) were only observed in the pleural effusion.

Other resistance mechanisms can be the acquired mutation of *EGFR* p.T790M, a MET receptor tyrosine kinase amplification, or *PIK3CA* mutations.[4,6] Regarding the patient, *EGFR* p.T790M was not detected nor was any other mutation in this gene except the exon 19 deletion, and in any case, osimertinib is effective with the p.T790M mutation. Interestingly, a deletion was found in *TP53* and *RB1* was mutated, which was found with a high prevalence in a SCLC genome sequencing study.[7]

C-SCLC is categorised as a subset of SCLC in the last WHO classification (2015).[8] C-SCLC is defined as a tumour with predominant features of small cell carcinoma with a minor (5% or less) component of any histological types of NSCLC. The incidence of C-SCLC among SCLC ranges from 5% to 28% depending on the studies, the type of specimen, and the size of the biopsy.[9,10] For example, among 22 C-SCLC cases diagnosed, only 5 were identified in small biopsies or cytological samples as bronchial biopsy, fine needle aspiration or lymph node biopsy.[9] Luo et al. described the absence of diagnosis of C-SCLC in 13 bronchial biopsy, 5 sputum or brushing cytology, and 3 percutaneous transthoracic needle aspiration biopsies where the corresponding surgical tissue confirmed the diagnosis. The presence of malignant pleural effusion is higher in C-SCLC than SCLC. In our case, only the pleural effusion allowed the diagnosis of C-SCLC with two populations having different cytological and immunophenotypic profiles.

In conclusion this is the first report of combined SCLC transformation identified from pleural effusion, after treatment with osimertinib as second line therapy. This evolution could explain the poor outcome for this young woman.

AUTHOR CONTRIBUTIONS

DF, EK, and JPD: Data collection. DF: Writing the manuscript. EK, PR, and JPD: Reviewing the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

INFORMED CONSENT

The patient described in the case report give her consent to publish data.

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