Navigating into the deep of molecular profiling of NSCLC

Alessandro Leonetti, MD, PhD
Parma, Italy

BACKGROUND

G.E. is a 67-year-old male with a smoking history of 40 pack-years and a negative familial history of cancer.

He presented with hemoptysis, cough, dyspnea, pain in the left chest wall, and a 13 kg weight loss over the past four weeks.

Among comorbidities: hypertension, type 2 diabetes mellitus, and benign prostatic hyperplasia.

Due to these symptoms, he was admitted to the ER.

A total body CT scan revealed a 75x51mm mass in the left lower lobe with pleural thickening, pleural effusion in the left cavity, homolateral mediastinal adenopathy, 29x19mm left chest wall subcutaneous lesion, and a 28x24mm nodule in the right adrenal gland (Figure 1a-d).
CURRENT PRESCRIPTIONS
- prednisone 25mg bid for dyspnea
- lansoprazole 30mg qd
- metformin 500mg qd
- tamsulosin 0.4mg qd

COMORBIDITIES
- hypertension
- type 2 diabetes mellitus
- benign prostatic hyperplasia
No relevant medical history.

OVERALL DIAGNOSIS
Left chest wall subcutaneous lesion: large cell carcinoma of the lung with rhabdoid phenotype. TTF-1 (-), CK-CAM5.2 (+), Cytokeratin 7 (-), Vimentin (+), P40 (-), PAX-8 (-).

TESTING
Initial molecular profiling showed MET amplification (MET copy numbers/nucleus>8; MET-to-CEP7: 3 per nucleus; Figure 2), in the absence of EGFR and MET exon 14 skipping mutations and ALK/ROS1 rearrangements.

The expression of PD-L1 was 90% (clone SP263, Ventana).

The NGS analysis by Myriapod NGS-LT 56G Oncopanel revealed a BRAF V600Q mutation, a TP53 W91* mutation and a STK11 mutation (Figure 3).
Due to CT scan evidence (3 months) and worsening (6 months) of symptomatic interstitial pneumonitis (Figure 8), high-dose steroids were started and pembrolizumab was interrupted after seven cycles, even if a lung, pleural and adrenal gland response was achieved.

**Figure 8:** a) appearance of asymptomatic GGO 3 months after the starting of pembrolizumab; b) evidence of symptomatic interstitial pneumonitis which required suspension of pembrolizumab and starting of high-dose steroids; c) improvement of interstitial pneumonitis one month after the starting of steroid.

During immunotherapy, the patient experienced hyperthyroidism, seven months after the last dose of pembrolizumab, the diagnosis of pemphigus was done. Moreover, a prostate adenocarcinoma (Gleason score 6) was diagnosed.

**PHYSICAL EXAM FINDINGS**
- pain in the left hemithorax, at the level of subcutaneous lesion

**LABS/IMAGING**
- see CT scan Figure 9

**DIAGNOSIS**
- progression of disease

**FOLLOW-UP TIMING**
- After 6 months, the patient presents with vertigo, postural instability, diplopia.

After 19 months from the start of pembrolizumab, the patient experienced oligo-PD at rights adrenal gland and left pleural lesion, which was treated with SBRT (Figure 9).
Want to learn more about this case? 

VOTE FOR CASE 01

- Speculate about the molecular landscape of the tumor in order to predict which treatment regimen would be more effective.

The detection of a pathogenic BRCA1 mutation at high allele frequency made us interrogate about its origin (germline vs somatic) and its potential implication in the tumour's genomics. The BRCA1 185Gfs*9 mutation is not described in any of the germline databases, leading us to familiar counselling.

We evaluated RAD51 and BRCA1 status by immunofluorescence on biopsies obtained at diagnosis and at progression to chemotherapy. In both samples, the absence of RAD51 foci defined an HRD status. Nevertheless, BRCA1 was detected in 40% of tumor cells, and this observation excluded a BRCA1 implication in lung cancer pathogenesis.

Although BRCA-1 mutation was not correlated to lung cancer pathogenesis, it was supposed to have a role in prostate cancerogenesis. Nevertheless, the tumor turned out to harbor HRD through RAD51 assay. Having excluded BRCA1 deficiency as the cause of HRD, this could be a consequence of the mutation in RAD51D. HRD status probably caused by RAD51D mutation could explain the major response to immunotherapy.

- Choose the preferred treatment regimen among re-challenge with immunotherapy, chemotherapy, and targeted therapy.

The patient started off-label use of Olaparib, achieving progressive disease as best response after three months.

FOLLOW-UP

Following progression of disease, the patient developed acute kidney failure due to caval vein compression and infiltration of right renal vein with subsequent clinical deterioration.