

THE AMAZING CASE RACE

Case Study 01

2023

ACADEMY

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INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER

Navigating into the deep of molecular profiling of NSCLC

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LEARNING GOALS

Goal 1: Understand the importance of comprehensive tumor genetic profiling.

Goal 2: Choosing tailored treatment strategies for the management of metastatic disease.

Goal 3: Learn how to manage immune-related adverse events.

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**).



Figure 1a. Left lower lobe mass

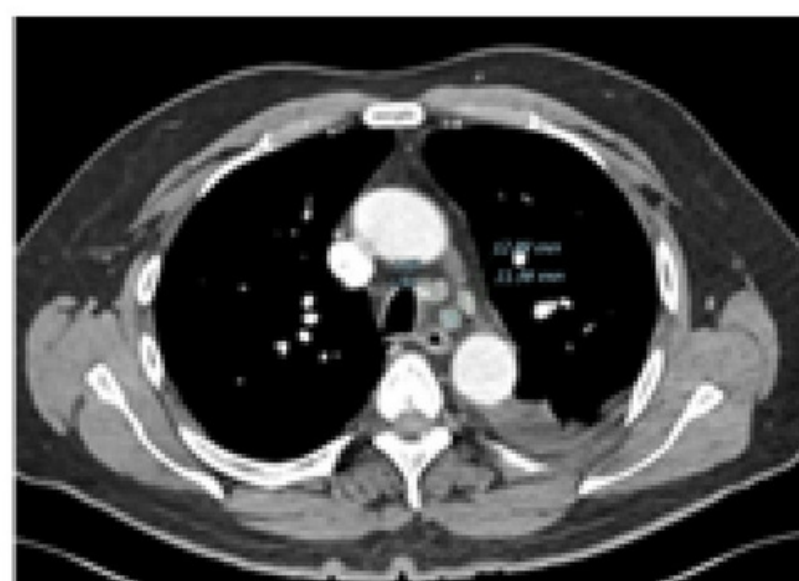


Figure 1b. Left paratracheal lymph

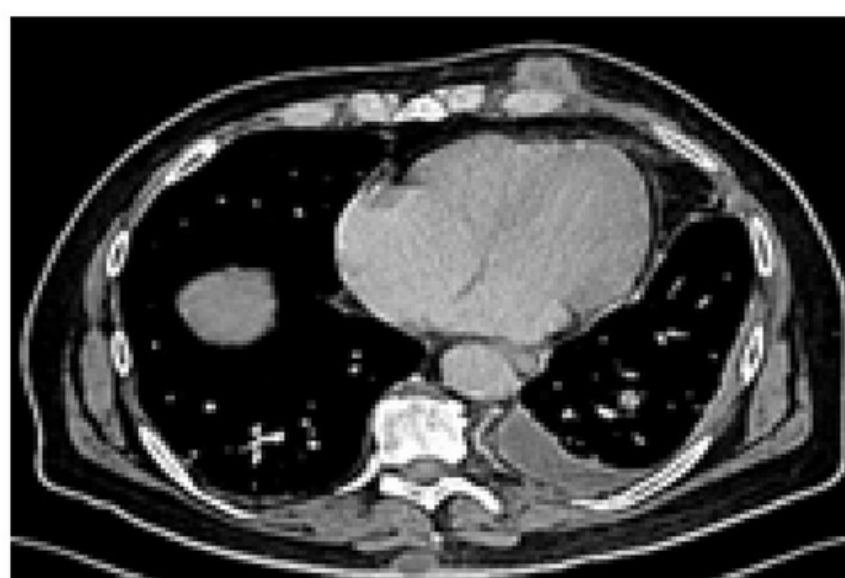


Figure 1c. Left pleural effusion; left chest wall subcutaneous lesion



Figure 1d. Right adrenal metastasis

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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).

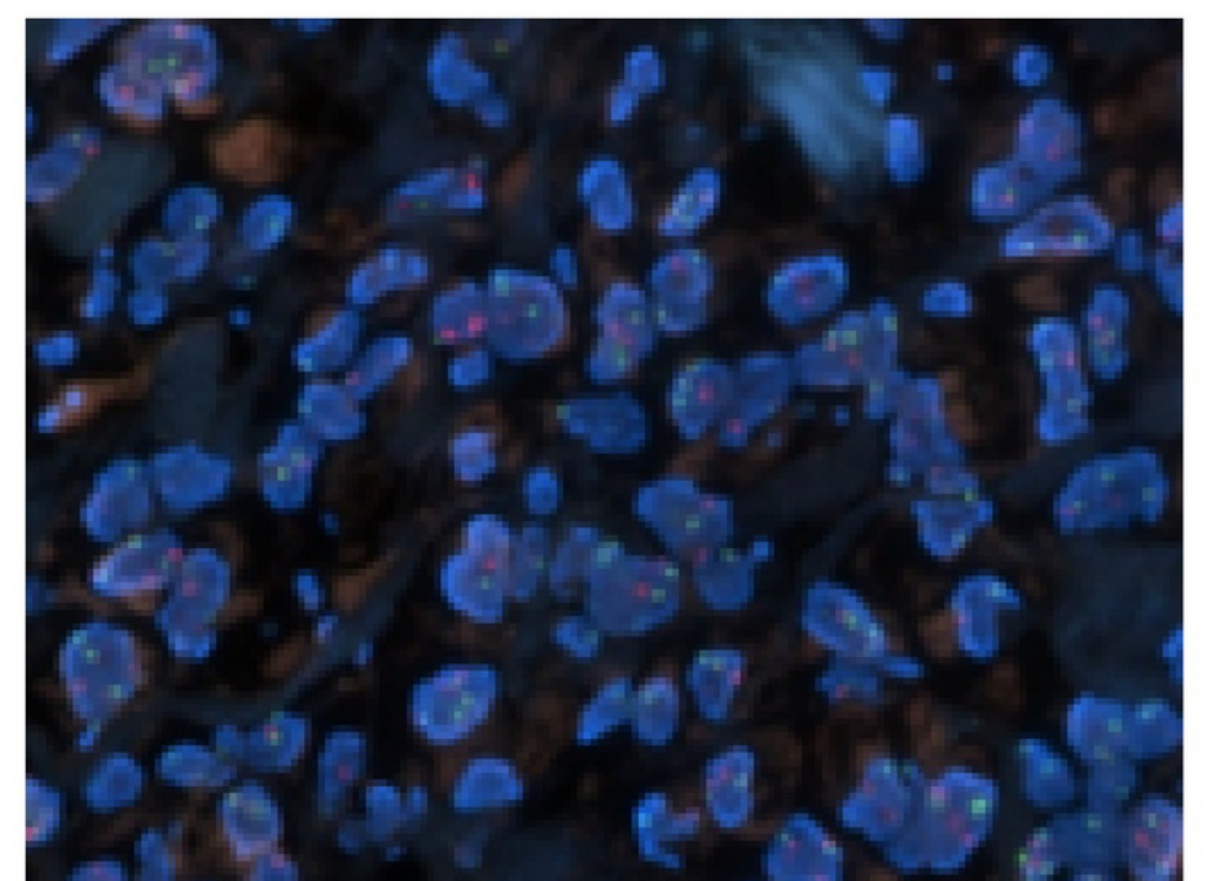


Figure 2. FISH for METamp

Gene	Frame	cDNA	Change (nucleotide)	Effect	Freq. allele	Clonality	Filter
BRAF	15	L1781_T1782G	GAGGCGG	missense, var.	27.52	Pathogenic	01/10
TP53	8	L270>A	GTTGTT*	stop_gained	27.87	Pathogenic	01/10
STK11	8	L1402C	GAGGCGG	missense, var.	10.8		01/10

Figure 3. NGS analysis by Myriapod NGS-LT 56G Oncopanel

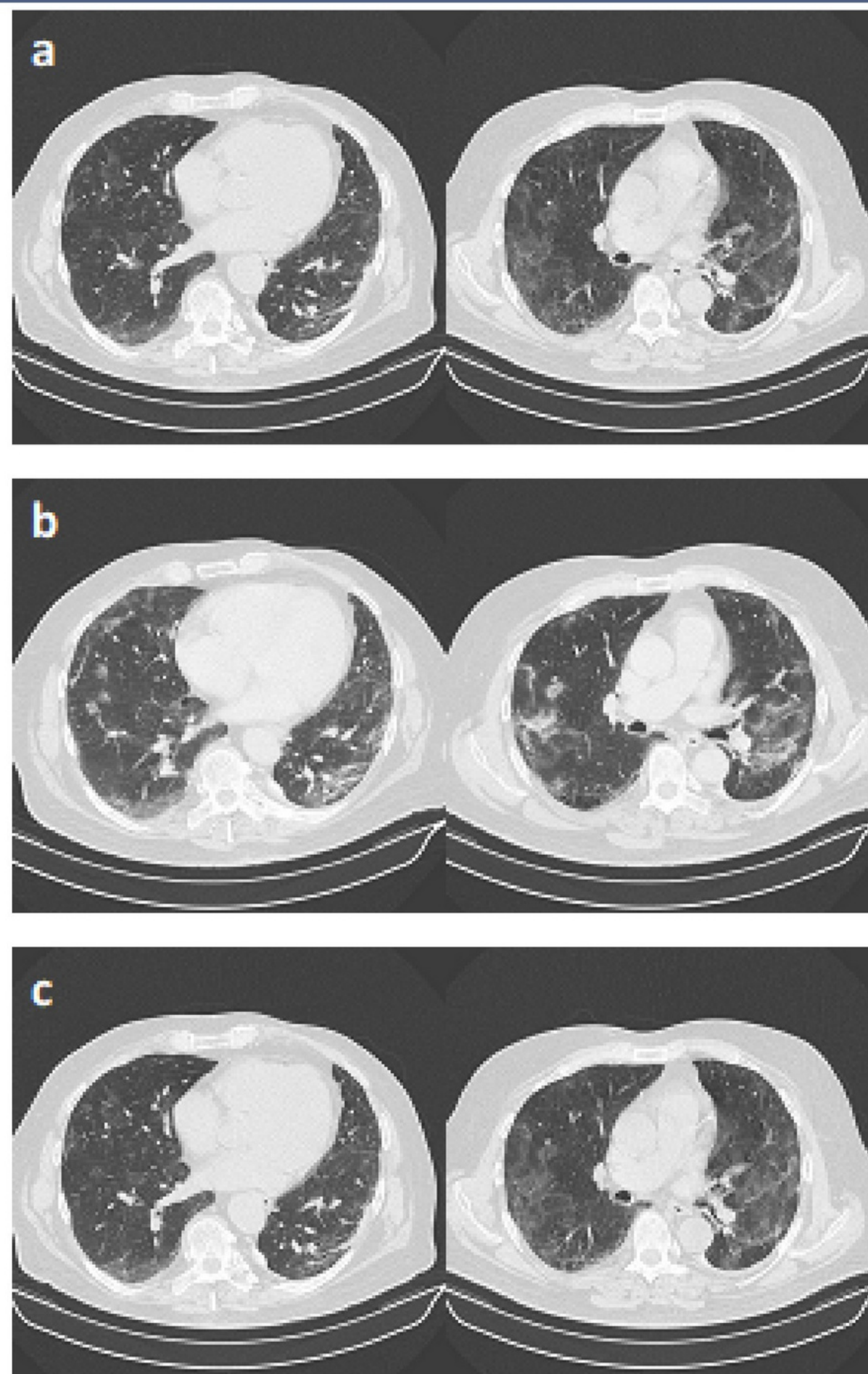
The NGS analysis by Myriapod NGS-LT 56G Oncopanel revealed a BRAF V600Q mutation, a TP53 W91* mutation and a STK11 mutation (**Figure 3**).

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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.

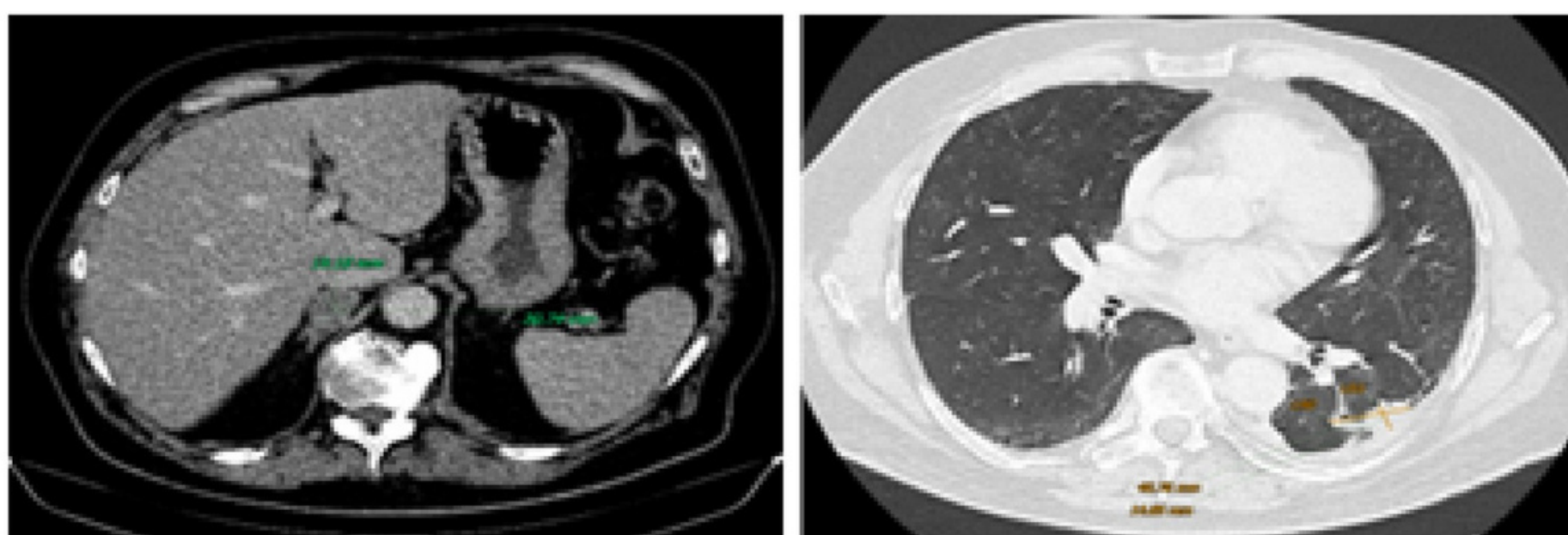


Figure 9. Right adrenal (Left) and left pleural (Right) oligo-PD

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**).

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.



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• Speculate about the molecular landscape of the tumor in order to understand tumor carcinogenesis and choose potential personalized treatments.

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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.