CARIS® | MOLECULAR TUMOR BOARD

Caris Molecular Tumor Board: Case Study

The Caris Molecular Tumor Board (CMTB) works directly with oncologists to interpret molecular findings and discuss treatment strategies for difficult-to-treat cases. Read how the CMTB approached a patient with a metastatic adenocarcinoma of unknown primary.

Background

While the diagnosis of a metastatic tumor of unknown primary can be devastating, classification of the tumor of origin and discovery of the tumor's molecular vulnerabilities can offer effective therapeutic interventions and identify optimal treatments. This requires thorough interrogation of the patient's tumor for a complete landscape of the molecular features and interpretation of the molecular information. In challenging cases, a multidisciplinary expert group like the CMTB can leverage broad expertise to identify potential therapeutic approaches.

Presented Case

- 24-year-old female patient.
- 6 months post-partum.
- Family history of pancreatic cancer (maternal grandfather) and breast cancer (two maternal great aunts), but mother's germline testing was negative for pathogenic *BRCA1/2* mutations.
- Presented with abdominal pain to the ER where imaging revealed asymmetric breast size, suggestive of multifocal breast cancer, and multiple liver masses.
- Subsequent imaging revealed a hypodense mass along the pancreatic head, ascites in the abdomen and pelvis, and trace bilateral pleural effusions.

Treatment and Molecular Profiling

- Due to the aggressive and advanced stage of the disease, patient started on carboplatin and paclitaxel for unknown primary while awaiting results.
- A liver biopsy, submitted as breast cancer, was sent to Caris for comprehensive molecular profiling to validate the tumor of origin and aid in clinical decision making.
- Whole exome sequencing (WES) and whole transcriptome sequencing (WTS) did not identify any actionable biomarkers.
- Immunohistochemistry analysis for ER, PR, and HER2 were all negative, consistent with a triple negative breast cancer diagnosis.
- Given two potential primary origins (pancreas or breast), a deeper analysis of the literature, genetic and transcriptomic data, alongside additional immunohistochemistry was evaluated.
- The following evidence was considered:
  - The rate of triple negative breast cancer is higher in patients with gestational breast cancer,[1] and previous case studies have reported gestational neuroendocrine breast cancer.[2]
  - Immunohistochemistry markers for neuroendocrine tumors (synaptophysin, chromogranin A, insulinoma-associated protein 1 [INSM1]) were positive.
  - Immunohistochemistry markers for breast (GATA3, mammaglobin) were negative.

The Caris Molecular Tumor Board (CMTB)

The CMTB provides oncologists with the opportunity to interact with leading cancer experts from across the country to obtain interpretation of molecular findings and therapeutic guidance for individual patients. This proprietary virtual tumor board platform is an innovative, real-time approach to deciphering complex data and treatment decisions on difficult-to-treat cases. The efficient access to cutting-edge information provided by the CMTB allows oncologists to focus their efforts on what matters most – developing the most informed personalized treatment strategies for their patients. Please visit **www.CarisLifeSciences.com/CMTB** to register and submit a case for review.

- Gene Set Enrichment Analysis (GSEA) of the tumor demonstrated an enrichment for pancreatic beta cell gene expression, as well as increased expression of genes associated with pancreatic neuroendocrine cancer.[3]
- Based on these findings and the imaging data indicating a mass in the pancreas, the tumor of origin favored pancreatic neuroendocrine carcinoma versus neuroendocrine breast cancer (a rare subtype of triple negative breast cancer).
- The E-karyotype revealed 9p21.3 arm loss, potentially resulting in loss of *MTAP, CDKN2A, CDKN2B,* and *CD274* (encodes PD-L1).
- The tumor was negative for PD-L1 (22c3).

CMTB Recommendation

In this diagnostically challenging case of neuroendocrine pancreatic cancer, the CMTB recommended a combination of etoposide with cisplatin with or without an antimetabolite, such as FOLFIRINOX, based on case reports.[4] While the CMTB noted that 43% of pancreatic neuroendocrine tumors had a response to ipilimumab with nivolumab,[5] they also highlighted the absence of PD-L1 (22c3) protein expression and potential deletion of *CD274* in this patient's tumor. If *MTAP* loss is confirmed by IHC, the CMTB recommended exploring clinical trials focused on MTAP-deleted tumors, including NCT04794699 (IDE397, MAT2A inhibitor), NCT03435250 (AG270,[6] MAT2A inhibitor) and NCT05094336 (AMG193, PRMT5 inhibitor). Based on the young age of the patient, the CMTB recommended a comprehensive germline test to determine the presence of pathogenic mutations associated with hereditary cancer syndromes.

Methylthioadenosine Phosphorylase (MTAP)

- *In vitro*, cancer cells with *MTAP* homozygous deletion are sensitive to loss of methionine adenosyltransferase II alpha (MAT2A) or the arginine methyltransferase, PRMT5.[8]
- *In vitro*, inhibition of MAT2A also inhibits PRMT5, resulting in DNA damage.[9]
- Patient-derived xenograft (PDX) preclinical models that are *MTAP* deleted demonstrate synergy with the MAT2A inhibitor AG270 and taxanes.[9]
- Several clinical trials are currently evaluating this synthetic lethality strategy by inhibiting MAT2A and PRMT5 in *MTAP*-deleted tumors.

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