

Limited Changes in the CNS Immune Microenvironment in Patients with Breast Cancer Metastasis to CNS and Capturing these Changes using Machine Learning. - Abstract # 1092

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Background

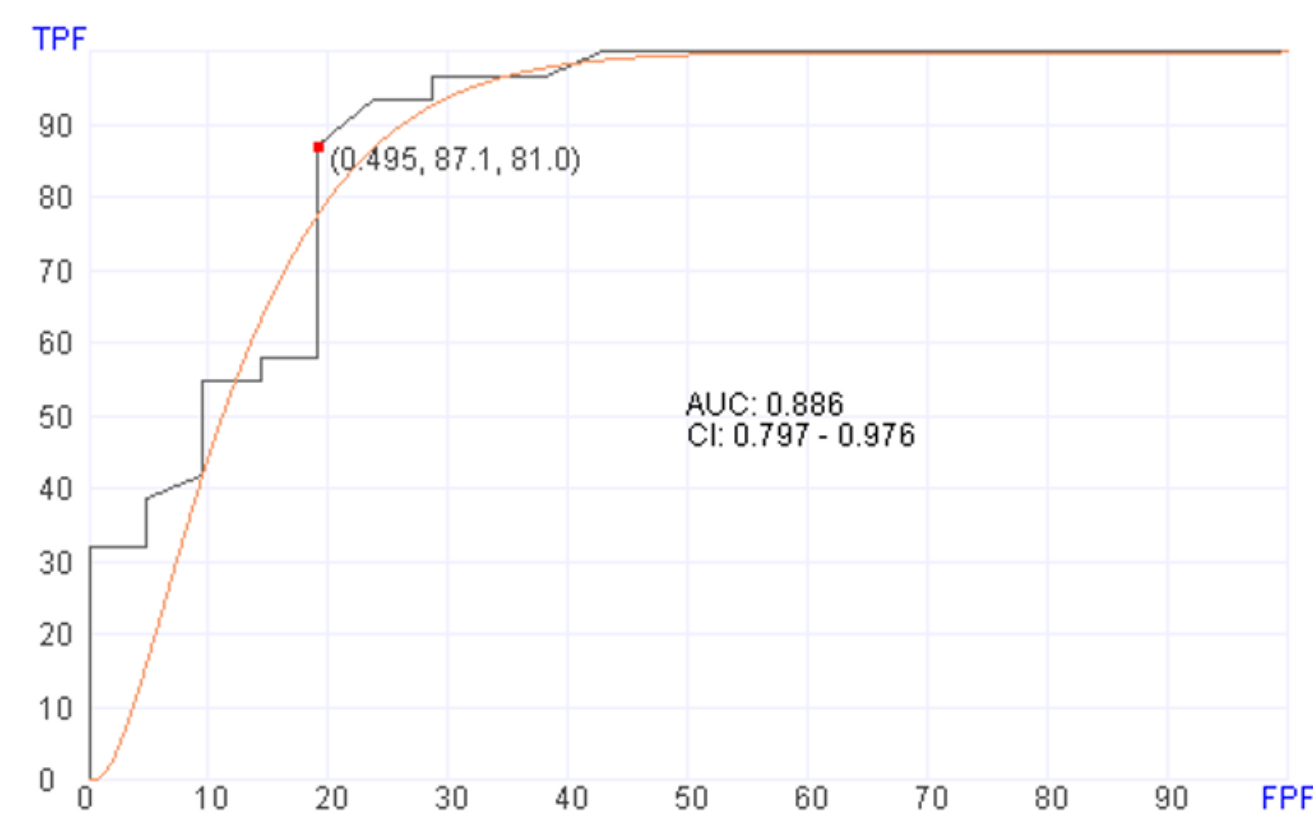
The central nervous system's status as an immune-privileged site means that the local immune microenvironment may contribute to the relatively high incidence of the CNS as a site of breast cancer metastasis, especially in aggressive subtypes like triple-negative and HER2+ tumors. To better understand this, we examined the transcriptomic profile of cells in the CSF of patients with and without CNS metastasis, seeking to identify relevant immune characteristics.

Methods

- RNA extracted from CSF cells of 156 patient samples. This included 63 with involvement by breast cancer and 93 with no evidence of CNS involvement (CSF-Pos and CSF-Neg, respectively)
 - The absence of metastatic tumor was confirmed by cfDNA testing
 - 63 CSF-Pos samples
 - 93 CSF-Neg samples
- The RNA was sequenced and quantified using a targeted panel of 1600 genes by NGS
- A machine learning algorithm (Bayesian statistics with k-fold cross-validation (with k=12)) was utilized to rank the top biomarkers distinguishing between CSF-Pos and CSF-Neg.
- Random forest was then used for distinguishing between the two classes using the top 30 ranked biomarkers.

Results

- Machine learning algorithm using 30 genes reliably distinguishes between CSF-pos from CSF-neg



Class	Precision	Recall	F1-score
CSF-Neg	0.773	0.810	0.791
CSF-Pos	0.867	0.839	0.852

- Majority of top 30 genes selected by the ML algorithm are involved in T-cell activation
- Despite this, only 5 of the 30 selected genes were expressed at significantly higher levels in CSF-Pos samples (after adjustment)

List of the 30 genes distinguishing between CSF-Pos vs CSF-Neg:
CCNB1IP1, HOXC11, TBX21, NFATC2, RCSD1, CD3D, INPP5D, CD5, TFG, NUTM2B, IKZF3, BIRC3, KRT19, KRT8, MAD2L1, MEF2B, NT5C2, MAPRE1, CD24, FLT3LG, LRP5, LAMP1, NFYC, APLP2, PATZ1, HSP90AB1, MAP3K6, NACA, CENPU, PTPN6

- No statistically significant difference between CSF-Neg and CSF-Pos in T-cells, B-cells, plasma cells, natural killer cells, neutrophils, monocytes, or dendritic cells (after adjusting for multiple testing)
- However, CSF-Neg is predominantly T-cells
 - Median CD2:CD22 RNA ratio
 - CSF-Neg: 70.07 TPM (range 0.01-14820)
 - CSF-Pos: 41.31 TPM (range: 0.4-10172)
 - No significant difference (P=0.19)
 - Median CD4:CD8A RNA ratio:
 - CSF-Neg: 4.89 TPM (range: 0.47-2522)
 - CSF-Pos: 5.0 TPM (range: 0.29-48)
 - No significant difference (P=0.31)

Conclusions

- While major CSF cell populations were similar between patients with and without CNS breast cancer metastasis, the CNS immune microenvironment undergoes subtle but significant transcriptomic changes that differentiate patients with and without CNS metastasis.
- A machine learning algorithm identified a 30-gene signature in CSF cells that effectively distinguishes between these patients with and without CNS metastasis, highlighting the potential for biomarker discovery.
- The majority of the top 30 genes are implicated in T-cell activation, suggesting a specific T-cell response within the CNS in the presence of metastasis.

Future Directions for Research

- Further investigation into the functional roles of these key genes may reveal novel targets for immunotherapy in patients with breast cancer brain metastases.