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Choroid plexus (CP) forms an anatomically functional barrier between the blood and cerebrospinal fluid (CSF) that dictates the cellular and humoral composition of the CSF. The immunological response of CP to inflammatory stimuli, such as cancer, remains unclear. Here, we find that CP orchestrates the immune composition of CSF in the steady state as well as in the presence of metastatic cancer. We show that the circulation-derived leptomeningeal monocyte-macrophages entering the CSF through CP promote the growth of leptomeningeal metastasis (LM) by perturbing the environment with a storm of dozens of pro- and anti-inflammatory cytokines. Functional manipulation of Type II Interferon pathway specifically within inflamed leptomeninges revealed that IFN-γ can serve as a dominant signal, further recruiting peripheral myeloid cells and activating their protective anti-tumoral response. This preclinical strategy was sufficient to controll the growth of syngeneic LM cancer cells and delay the onset of lethal LM.

LMD-17. NEOPLASTIC MENINGITIS IN LUNG CANCER: RETROSPECTIVE REVIEW OF CLINICAL FEATURES, DIAGNOSIS AND OUTCOME IN ADULT PATIENTS.

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BACKGROUND: Neoplastic Meningitis (NM) is a lethal complication of cancer. Its incidence is rising and in 10% of the cases NM is the first manifestation of the disease. Diagnosis relies on the clinical manifestations, neuroimages, and finding of malignant cells in cerebrospinal fluid (CSF). Diagnosis is often challenging due to the low sensitivity of the different diagnostic modalities. The aim of this study is to identify the clinical features, diagnosis, treatment and outcome of lung cancer patients with NM. METHODS: Clinical records from patients with diagnosis of lung cancer and NM between 2011–2021 were retrospectively reviewed at a tertiary neurological center in Buenos Aires, Argentina. RESULTS: Twenty-seven patients were included. Median age was 58 years (IQR 52–64). 17 (65%) were female. Twenty-four patients had non-small cell lung cancer (91% adenocarcinoma), two had neuroendocrine lung cancer and one small cell lung cancer. In 19 (70%), meningeal involvement was a result of progressive disease from previously diagnosed cancer. In 12 (44%) patients meningeal disease developed posterior to parenchymal brain metastases surgical approach, 5 (41%) with posterior fossa craniotomy. Headache was the most frequent symptom (53%). CSF analysis was abnormal in 13 (48%) patients, with positive cytology in 10 (37%). Meningeal enhancement was detected with magnetic resonance imaging of brain or spine in 24 (92%) patients. Twenty-one (77%) patients received oncological treatment, 14 (51%) with chemotherapy (8 systemic, 3 intrathecal and 3 intrathecal plus systemic). Thirteen (48%) patients underwent treatment with either immunotherapy or target-therapy. 11 patients underwent whole brain radiotherapy. Median overall survival was 7 months (CI 95%: 3.5–10.4). CONCLUSION: Headache was the most frequent symptom. Ninety-two percent of patients had meningeal pathological enhancement in high-quality MRI with gadolinium contrast of brain and spine. Despite median survival was poor (7 months), small subsets of these patients (22%) survived more than 2 years.

LMD-18. DETECTION AND SERIAL MONITORING OF CSF CTDNA IN BREAST CANCER LEPTOMENINGEAL DISEASE (BCLM)

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BACKGROUND: CSF cytology is the gold standard diagnostic test for BCLM, but is hampered by a low sensitivity, often necessitating repeated lumbar puncture to confirm or refute the diagnosis. Furthermore, during the treatment of BCLM, there is no robust quantitative response tool to guide treatment decisions. Material and METHODS: cfDNA was obtained from CSF and plasma in patients with breast cancer undergoing investigation for BCLM (n = 28) and during subsequent intrathecal treatment (n = 13). Ultra low pass whole genome sequencing (ulpWGS) and estimation of the ctDNA fraction was performed. Results were validated by mutation-specific digital droplet PCR (ddPCR). RESULTS: 22/28 cases had confirmed BCLM by positive MRI and/or CSF cytology. The remaining 6/28 had suspected but non-confirmed BCLM, and at median 20 months follow up, these patients were BCLM-free. CSF ctDNA fraction was significantly elevated (median 57.5, IQR 38.3 - 84.9%) in confirmed BCLM compared to 6 non-confirmed BCLM (median 5.0, IQR 0.0 - 6.7%) (p <0.0001). ctDNA fraction was detected in BCLM confirmed cases regardless of negative cytology or MRI. Plasma ctDNA fraction was only detected in extra-cranial disease progression. ctDNA fraction was concordant with mutant allele fraction measured by ddPCR (n = 118 samples). Serial CSF ctDNA fraction during intrathecal treatment showed dynamic changes, while CSF cytology and MRI were often unchanged or equivocal. Early reduction in CSF ctDNA fraction was associated with longer responses to intrathecal therapy. Further, rising ctDNA fraction during intrathecal chemotherapy could be detected up to 6 weeks before relapse in neurological symptoms, cytology or MRI. CONCLUSION: Measuring CSF ctDNA fraction is a sensitive diagnostic test for BCLM and could lead to more timely and accurate diagnosis. During intrathecal chemotherapy, CSF ctDNA also provides a quantitative response biomarker to help guide clinical management in this difficult treatment scenario.

LMD-19. ANATOMIC AND SURGICAL FACTORS PREDICT DEVELOPMENT OF LEPTOMENINGEAL DISEASE IN PATIENTS WITH METASTATIC MELANOMA

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BACKGROUND: Leptomeningeal disease (LMD) is a devastating complication of systemic malignancy, portending a poor prognosis with an estimated median survival of 4–6 weeks if left untreated. Several reports have suggested surgical resection, particularly piecemeal resection, as a potential causative factor. Herein, we explore if surgical and anatomical factors are correlated with development of LMD in patients with melanoma brain metastases. METHODS: Patients treated at our institution between 1999–2019 for primary melanoma with brain metastasis were compiled into a database based on ICD9/10 coding. 1,079 patients with melanoma brain metastases and appropriate imaging were identified, and 834 patients with a minimum of 3 months' follow up were included. Patients were dichotomized by development of LMD or lack thereof. General demographic information, surgical and anatomic data, and ventricular access during surgery were investigated as possible correlative factors for the development of LMD. RESULTS: On univariate analysis, female gender (p=0.033), presence of dural metastasis (p=0.018), presence of periventricular lesions (p<.001), presence of intraventricular lesions (p<.001), and ventricular access during surgery (p<.001) were significantly associated with LMD. Patients undergoing surgery, or those undergoing surgery without ventricular access, were not at higher risk of LMD. Administration of immunotherapy, either as first-line or salvage therapy, did not impact rates of LMD. On multivariate analysis, female gender (p=.033), presence of periventricular lesions (p<.001), presence of intraventricular lesions (p<.002), and presence of dural metastasis (p=0.032) were significantly associated with development of LMD. In patients who had surgery, iatrogenic ventricular access (p<.001) was significantly correlated with LMD. CONCLUSIONS: In a retrospective cohort of patients with melanoma metastatic to the brain, those patients with pre-existing lesions in contact with the CSF space are more likely to develop LMD than those who do not. In addition, iatrogenic access to the CSF space during surgery is highly correlated with LMD development.

LMD-20. IMMUNE SUPPRESSIVE MACROPHAGES AND SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3) EXPRESSION ARE COMMON IN MELANOMA LEPTOMENINGEAL DISEASE

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Leptomeningeal disease (LMD) in melanoma patients is associated with significant neurological impairments and has a dismal outcome with a median survival of 1.8 months. Despite the therapeutic benefit of targeted therapies and immunotherapies for most kinds of Stage IV melanoma, patients with LMD do not typically benefit. A deeper understanding of the tumor microenvironment (TME) of LMD may provide more appropriate therapeutic selection. A retrospective analysis of subjects who underwent surgical resection with LMD (n=8) were profiled with seven color multiplex to evaluate the expression of the global immune suppressive hub - the signal transducer and activator of transcription 3 (STAT3) and for the presence of CD3 T cells, CD68+ monocytes, CD163 immune suppressive macrophages, CD11c+ antigen presenting cells (APCs) in association with the melanoma tumor marker S100B and DAPI for cellular nuclear identification. High-resolution cellular imaging and quantification was conducted using the Akoya Vectra Polaris. CD163+ macrophage is the most frequent immune cell population in the LMD TME. Occasional CD3+ T cells and CD11c+ APC are also identified, although the latter has concurrent expression of CD163. STAT3 nuclear localization is heterogeneously expressed in the various immune cell populations. Occasional immune cluster interactions can be seen in the tumor stroma and the tumor edge. In conclusion, the TME