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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 control 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:** ctDNA 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

of LMD is largely devoid of CD3+ T cells, but is enriched for immune suppression and innate immunity.

LMD-21. HEADACHE IMPROVEMENT PREDICTS SURVIVAL AFTER CSF DIVERSION IN LEPTOMENINGEAL DISEASE

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BACKGROUND: Leptomeningeal carcinomatosis (LMD) is a seeding of the leptomeninges by malignant cells. Clinical, treatment and patient-related factors have been described in patients with LMD. Current data are limited by small sample size, particularly in patients undergoing ventriculoperitoneal shunting (VPS) as part of the treatment regimen. **OBJECTIVE:** This study presents the largest cohort of LMD patients in the literature undergoing cerebrospinal fluid (CSF) diversion and seeks to identify prognostic factors related to survival. **METHODS:** A retrospective review of patients diagnosed with LMD between 2010 and 2016 at a quaternary referral center was performed. Cox proportional hazards modeling was utilized to identify variables associated with improved overall survival from LMD diagnosis. Overall survival was depicted using Kaplan-Meier methodology. Competing risk methodology was used to identify variables associated with VPS, considering death as a competing event. **RESULTS:** Of the 314 patients identified, 112 underwent VPS placement. The median overall survival from LMD diagnosis was 3.9 months (95% CI: 3.2–4.4). The presence of headaches, increased opening pressure, and gait difficulty increased the likelihood of VPS placement (all $p < 0.05$). VPS, older age, lower Karnofsky Performance Status (KPS), higher opening pressure and CSF nucleated cell count (NCC) increased the risk of death (all $p < 0.05$). Patients reporting headache improvement after VPS had better survival ($p < 0.05$). **CONCLUSIONS:** Headache, increased opening pressure and gait instability were associated with higher rate of VPS placement and may portend more aggressive disease. Headache improvement following VPS is a favorable prognostic sign, suggesting survival advantage for patients with hydrocephalus undergoing VPS. Age, KPS, VPS, opening pressure, CSF NCC, concomitant visceral metastases and histology-specific molecular profile impact survival.

LMD-22. CLINICOPATHOLOGICAL SPECTRUM OF LEPTOMENINGEAL METASTASES: A 3 YEAR RETROSPECTIVE STUDY

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OBJECTIVES: Cytological examination of cerebrospinal fluid is a widely used cost effective, simple procedure and a reliable routine diagnostic test. CSF cytology helps in detection of inflammatory diseases of the CNS, diagnosis of subarachnoid haemorrhage and the identification of malignant cells in metastatic or rarely primary CNS malignancies. Leptomeningeal metastases (LM) is estimated to occur in 5% of all patients with cancer. It has a higher propensity to occur in solid tumours compared to haematological malignancies. In view of poor prognosis, early diagnosis may aid in appropriate tumour staging and aggressive therapeutic intervention. **METHODS:** All the samples of CSF received in the Department of Laboratory for cytological examination and reported as 'positive for malignant cells' during the year January 2018 to December 2020 were included in the study. All the cases were routinely evaluated on Neubauer's chamber, direct smear and a cytospin preparation stained using MGG stain. The clinical records and any further ancillary testing performed were retrospectively analysed. **RESULTS:** 87 cases with LM were identified over 3 year duration. Mean age of presentation was 43 years. Metastatic solid malignancies (56%) had a higher incidence of leptomeningeal metastases compared to haematolymphoid malignancies (40%) and CNS medulloblastomas (2%). Most common solid tumour with involvement of CSF was adenocarcinoma lung (51%) followed by breast carcinoma (37%). Of all the cases of adenocarcinoma lung with LM, EGFR mutant NSCLC were 40% while 8% showed ALK gene rearrangement. Amongst the haematological malignancies, acute leukaemia's constituted 67% of cases while systemic NHLs were 34%. Most of the cases (97%) presented with neurological symptoms during the course of treatment while 3 cases (3%) showed LM at the time of first presentation. **CONCLUSIONS:** With appropriate clinicoradiological correlation, CSF cytology remains the gold standard for identification of malignant cells in cases with already known primary tumour (leptomeningeal dissemination of the disease). In this study, clinical features of both solid and haematolymphoid malignancies were evaluated. The group of solid malignancies included adenocarcinomas lung, breast, gastrointestinal tract and renal cell carcinoma. With the availability of EGFR TKIs and ALK inhibitors, overall survival of the patients may be prolonged with therapeutic interventions despite limited CSF and CNS penetration of these drugs.

MEDICAL THERAPY (CHEMOTHERAPY AND IMMUNOTHERAPY)

THER-01. TARGETED THERAPY AND INTRACRANIAL METASTATIC DISEASE: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

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BACKGROUND: Targeted therapies have been hypothesized to prolong survival in the management of patients with intracranial metastatic disease (IMD), but, paradoxically, to increase IMD incidence by improving systemic disease control and prolonging survival from the primary tumor. The real-world benefits of targeted therapy in management of patients with IMD are unclear, as clinical trials have excluded patients with IMD and lacked endpoints reporting intracranial outcomes. **METHODS:** This retrospective cohort study included all patients in Ontario, Canada, diagnosed with IMD from 2005 to 2018 with primary diagnoses of breast cancer, lung or bronchus cancer, or melanoma, and control patients matched by primary disease without IMD. Kaplan-Meier and multivariable Cox regression analyses were performed to compare overall survival (OS) between patient sub-cohorts divided by primary disease and stratified by targeted therapy receipt or IMD status. **RESULTS:** Post-IMD targeted therapy was associated with prolonged OS in patients with HER2-positive breast cancer (HR 0.41; 95% CI, 0.33–0.5), EGFR-positive lung cancer (HR 0.28; 95% CI, 0.23–0.34), and BRAF-positive melanoma (HR 0.2; 95% CI, 0.14–0.29), compared to those who did not receive post-IMD targeted therapy. Presence of IMD was associated with shorter OS in patients with metastatic HER2-positive breast cancer (HR 1.8; 95% CI, 1.56–2.08) and metastatic EGFR-positive lung cancer (HR 1.22; 95% CI, 1.08–1.39) but not metastatic BRAF-positive melanoma (HR 1.11; 95% CI, 0.77–1.61), compared to those without IMD. **CONCLUSIONS:** Our findings show that real-world use of targeted therapies was associated with prolonged OS in patients with IMD in the setting of HER2-positive breast cancer, EGFR-positive lung cancer, and BRAF-positive melanoma. Inclusion of patients with IMD in clinical trials and use of endpoints that interrogate IMD will be critical to determine the role of targeted therapies in the management of patients with IMD.

THER-02. PARP INHIBITOR TOLERABILITY AND IMPACT ON PROGRESSION-FREE SURVIVAL IN PATIENTS WITH HIGH-GRADE, OVARIAN CARCINOMA WITH BRAIN METASTASIS: A CASE-SERIES

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Brain metastases secondary to ovarian carcinoma is an uncommon but increasing phenomenon. PARP inhibitors (PARPi) are increasingly used as an adjunctive treatment in patients with central nervous system metastases (CNS). Historically brain metastases has a historically poor prognosis. Five women with a mean age of 60.4 ± 7.6 years were included. All had stage IIIC/IV ovarian cancer and diagnosed with brain metastases at recurrence. Three underwent resection for oligometastatic disease followed by post-operative stereotactic radiosurgery (SRS), one had SRS without surgery, and one patient underwent whole brain radiotherapy for multiple metastases. Pathology was confirmed in those who were resected. Two patients had evidence of systemic disease in addition to CNS spread. Three women were BRCA1/2 Positive. Following initial radiotherapy, one patient received adjuvant chemotherapy followed by olaparib maintenance, one received 13 cycles of bevacizumab/olaparib, followed by olaparib maintenance. A third patient was treated with olaparib/bevacizumab and two patients received olaparib monotherapy, both of whom continued on therapy. All received olaparib therapy during their treatment and all had minor dose modifications due to side effects. Mean survival from initial cancer diagnosis was 62.4 ± 20.4 months. Mean duration of PARPi therapy was 27.6 ± 16.8 months. Mean survival following CNS recurrence was 22.8 ± 12 months. One patient is disease-free, two patients are alive with stable disease, one patient is alive but off treatment secondary to progression, and one patient is deceased secondary to progression of her brain metastases after being on PARP therapy for 18 months. The cohort remained highly functional across the trajectory of their disease with ECOG scores of 1 (n=4) or 0 (n=1). The results of this single institution retro-