Journal of Advances in Medicine and Medical Research

26(10): 1-13, 2018; Article no.JAMMR.41792
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Biomarkers for Carcinoma Meningitis in Solid Tumors

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Authors' contributions

This work was carried out in collaboration between both authors. Author AM wrote the first draft of the manuscript and managed the literature searches. Author RP reviewed the draft. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/41792
Editor(s):
(1) Abrao Rapoport, Professor, General Director of Heliopolis Cancer Hospital, Sao Paulo Unversity, Brazil.
Reviewers:
(1) Ebtissam Alerraqi, Egypt.
(2) Jose Francisco De Sales Chagas, Sao Leopoldo Mandic Medical School, Brasil.
(3) Arthur N. Chuemere, Univerity of Port Harcourt, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/25157

Review Article

Received 4th April 2018
Accepted 12th June 2018
Published 15th June 2018

ABSTRACT

Carcinomatous meningitis (CM), also known as neoplastic meningitis or leptomeningeal metastasis, refers to the invasion of meninges protecting the brain and spinal cord by tumor cells. It should be distinguished from brain metastasis where there is an infiltration of brain parenchyma by metastatic cells. Cancer cells from the primary source can migrate to the meninges through various ways: vertebral and paravertebral metastasis (breast and lung cancers), perineural spaces (gastrointestinal cancers), arteries from parenchymal metastasis, and rarely by direct invasion (primary central nervous system tumors). Patients often present with non-specific symptoms, like a headache and altered mental status, or focal neurological signs, depending on the area of the central nervous system involved. Due to poor prognosis and limited success in treating it, early detection is key. Diagnosis in suspected cases by cerebrospinal fluid (CSF) cytology (identifying malignant cells) and/or imaging has limited success. In this review, we discuss the need for using various biomarkers in CSF to increase the probability of a diagnosis of CM in solid tumors. Biomarkers can also help in predicting the disease burden, response to treatment, and in detecting

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the recurrence. We also discuss utilizing Fluorescence in situ hybridization (FISH), Rare cell capture technology (RCCT) and circulating tumor DNA (CtDNA) in identifying malignant cells in CSF for diagnosing CM.

Keywords: Carcinoma meningitis; biomarkers; cerebrospinal fluid; circulating tumor cells.

1. INTRODUCTION

Carcinomatous meningitis is a rare but severe complication of advanced cancers. It is characterized by multifocal seeding of the leptomeninges by malignant cells that originate from a solid tumor. With improved overall survival in a majority of cancers with advances in cancer management, more cases of CM are being diagnosed lately. In some cases, the blood-CSF barrier creates a sanctuary site, to shield tumor cells from systemic therapy [1].

In 1990, Kaplan *et al* reviewed 63 cases of CM confirmed by cytology, a majority of them had in solid tumors (49%) followed by leukemia (27%) and lymphoma(24%) [2]. Among the solid tumors, its incidence ranges from 5% to 8% in patients with metastatic cancers, however, undiagnosed or asymptomatic cases are frequently reported [3,4-10]. At autopsy, the frequency of CM averages 20 percent and is much higher with some tumor types [2,11,12]. Co-existing brain metastases are present in 50 to 80 percent of patients in modern series [13-17]. The most common solid tumors associated with CM are breast cancer (12 to 35 percent) with predilection to infiltrating lobular carcinoma, lung cancer (10 to 26 percent), melanoma (5 to 25 percent), gastrointestinal malignancies (4 to 14 percent), and cancers of unknown primary (1 to 7 percent) [3,4,18-20]. CM is rarely reported in prostate cancer [5]. Primary brain tumors can also infiltrate the leptomeninges by dissemination of tumor cells in cerebrospinal fluid [21,22]. Patients with vertebral and paravertebral metastasis have a relatively higher propensity of leptomeningeal involvement as the tumor cells can traverse venous plexus through subarachnoid space to finally involve leptomeninges [6].

Although the diagnosis is challenging, an early treatment before the setting of neurological deficits is required in order to improve the clinical outcomes and prolong survival by several months. A multidisciplinary approach is needed to manage CM, which varies with the type of primary tumor, previous lines of treatments and functional status of the patients. The treatment requires a combination of chemotherapy and targeted therapies administrated systemically or via the intra-cerebrospinal fluid route, surgery, and radiotherapy [1].

2. IMPORTANCE OF BIOMARKERS IN DIAGNOSIS OF CM

Traditionally, when patients with advanced stage cancers report suspicious neurological symptoms that cannot be explained by common causes, work up for CM is initiated. This investigation includes imaging studies like computerized tomography (CT) scan and Magnetic resonance imaging (MRI) scan, along with cerebrospinal fluid (CSF) analysis specifically for detection of tumor cells [7]. However, there are some concerns about the accuracy and effectiveness of diagnostic evaluation.

Firstly, the majority of symptoms are non - specific, which can be easily attributed to cancer related complications, like brain metastasis, and chemotherapy, related adverse effects. Secondly, CSF cytology has high specificity (>95%) but low sensitivity (<50%); moreover, about 40% of cytology negative patients have CM. Lastly, MRI findings are present in less than half of the patients with CM [8,9]. Few studies have reported that pertinent clinical features and imaging findings are sufficient to diagnose CM, even if CSF cytology is negative[10].

Kizawa, M *etal* collected 24 samples of spinal cords with a histo-pathological diagnosis of CM. Among 24 patients, only 29% (7) were diagnosed before death. Age of death among the patients studied ranged from 18 to 83. This raises serious questions about the effectiveness of currently available tools in diagnosing CM [11].

Identification of specific biomarkers of a disease may allow for earlier diagnosis and treatment of these aggressive disease presentations. In the following review focuses on the biomarkers associated with CM originating primarily from solid tumors.

3. CLINICAL PRESENTATION IN CM

Multifocal microscopic vascular changes are the hallmark of CM which explains the onset of

neurological signs and symptoms on presentation, which vary depending upon the site of nervous system involvement [12]. CM should always be included in the differential diagnosis while managing the patients with advanced cancers with neurological symptoms. As discussed earlier, underdiagnosis of CM is a major concern [8].

Presentation varies with primary tumor type. In leukemias and lymphomas, CM may present without any apparent systemic disease or even during remission. This is in contrast to solid tumors, where there is usually an evidence of metastatic disease [2].

Elevated intracranial pressure and meningeal irritation often involved in CM can give rise to an array of nonspecific symptoms, like a headache, nausea, vomiting, confusion, disorientation, and neck stiffness. When the spinal cord is involved, patients present with features related to radiculopathy, like back pain, leg pain sensory loss, weakness, and loss of bowel and bladder control. Hydrocephalus (both communicating and obstructive) can also occur if tumor deposits obstruct CSF outflow [11,13-15]. Cranial nerve involvement may manifest as diplopia, dysarthria, dysphagia, paresthesia, facial droop, and hearing loss, which are not uncommon [16]. Cortical irritation due to direct invasion of CM deposits or local edema may cause hemiparesis, vision deficits, and aphasia. Cerebellar involvement is also frequent [17].

4. DIAGNOSIS OF CARCINOMA MENINGITIS

4.1 Imaging

MRI is the most preferred imaging modality for CM. Enhanced leptomeninges along the cortical surface, cerebellum, basal cisterns, cranial nerves, spinal cord surface, and cauda equina, in addition to linear or nodular deposits in the subarachnoid space are typical features seen on MRI in CM. The T1-weighted (T1W) gadolinium-DTPA-enhanced MR (Gd-MR) and contrast-enhanced CT (CE-CT) were compared in a retrospective study, which showed Gd-MR to be more useful in CM when compared to CE-CT. As MRI is superior, CT should only be used in patients who cannot have MRI [18]. Brain 18F-Choline PET/CT can also be used in the diagnosis of leptomeningeal melanomatosis [19].

Among various MRI sequences available, sensitivity and specificity of contrast-enhanced T1-weighted MR sequences are higher than contrast-enhanced fluid-attenuated inversion recovery (FLAIR) sequences [20]. ^{111}Indium-DTPA CSF flow studies (FS) can identify CSF flow abnormalities. Sequential imaging is advised in patients with initial normal imaging and high suspicion of CM [21]. Diagnosis of CM by proton magnetic resonance spectroscopy (H MRS) was also described recently [22].

4.2 ROUTINE CSF ANALYSIS

In CM, elevated opening pressure, low glucose and high protein and cell count are common. These are non-specific findings seen in many other disease conditions, and moreover, cytology can be positive even if routine CSF findings are normal [2] It has been duly noted that site of the collection of CSF should be taken into consideration while determining reference values of CSF components, especially the tumor markers. The values of LDH, glucuronidase, β2-microglobulin, and CEA are higher in lumbar samples when collected through routine lumbar punctures, but the reference value of glucose is less when compared to ventricular CSF collected through an ommaya reservoir. CSF protein was found to be higher than normal levels in samples collected after intrathecal therapy. Similarly, caution must be taken while interpreting CSF tumor marker levels during therapy. These levels should be compared with test results with a reference range estimated for a specific region of the neuraxis, and bacterial or fungal infections should be excluded from the diagnosis by careful examination of the CSF [23].

4.3 Role of Cytology in Diagnosis of CM

Cytology performed in patients with suspected CM (with clinical features or by neuroimaging), known primary cancer, and those with unexplained high cell counts and protein levels may less likely miss the diagnosis of CM [24]. Therefore, patient selection is key in utilizing this test. Cytology has very high specificity but poor sensitivity, which means that we cannot rule out CM if cytology is negative [8,9]. The relatively low sensitivity of the CSF cytology prompted researchers to start exploring other ways to increase the diagnostic yield.

Waaserstrom *et al* studied 90 patients with CM based on clinical features and other tools. Although only half the patients had positive cytology at the beginning of the study, repeat analysis showed positive cytology in 90% of

cases [25]. Repeat cytological assessments are recommended if the index of suspicion is high.

Cytology testing can be combined with other tumor markers to increase the diagnostic yield. For instance, in solid tumors, a significant correlation exists with cytology with β glucoronidase in that there is a low possibility of CM in a patient with negative cytology and normal βglucoronidase. A similar correlation was demonstrated between β2-microglobulin and cytology in hematological cancers. While monitoring the therapy, the predictability of CSF tumor markers is more reliable if cell count is low [23].

The use of immunohistochemistry (IHC) with monoclonal antibodies was studied along with cytology in two major studies [26,27]. It has high specificity and poor sensitivity. By combining it with cytology, the sensitivity is increased by 8-10%.

4.4 CSF Protein Analysis

4.4.1 IgG index or oligoclonal IgG subfractions

In CM, the plasma cells that produce large amounts of IgG antibodies infiltrate the tumor deposits on meninges. Measuring the local IgG production by CSF IgG index (ratio of CSF IgG to CSF albumin) and compare it to the serum IgG to serum albumin ratio, identifies the local IgG production and can be utilized in supporting the diagnosis of CM [28,29]. The other disease conditions such as multiple sclerosis and neurosyphilis are also associated with high local IgG production and hence its interpretation must be done carefully.

4.4.2 Protein profiling

An interesting study was done in which researchers compared various proteins involved in adhesion and inflammatory process between patients with cytologically proven CM and those with other disease conditions, including systemic malignancies, meningitis (viral and aseptic), and other non-neurological diseases. They found patients with CM had high levels of Vascular Cell Adhesion Molecule-1 (sVCAM-1), soluble Intercellular Adhesion Molecule-1 (sICAM-1), Interleukin-8 (IL-8), Pulmonary and Activation Regulated Chemokine (PARC), Interleukin-18 (IL-18) and Interferon-γ inducible protein (IP-10). This study even suggested that higher levels of IL-8, PARC and, IP-10 were more specific to CM, and when combined with total protein and glucose levels, can be used to diagnose CM [30].

4.5 CSF Testing for Specific Biomarkers

4.5.1 CSF - gastrin releasing peptide

Small cell lung cancer (SCLC) cells are unique when compared to other lung cancer cells. They have neurosecretory granules that secrete various endocrine peptides, like gastrin releasing peptide (GRP), adrenocorticotropic hormone (ACTH), vasopressin, pancreatic polypeptide, neuron specific enolase as well as others. GRP is a 27-amino acid autocrine growth factor which increases mitotic activity in cancer cells and helps in its proliferation [31]. GRP has both diagnostic and prognostic value. In SCLC, suspected to be complicated by CM, CSF-GRP level is more than six times the serum-GRP level. This knowledge can be used in establishing the diagnosis of CM in suspected SCLC patients with negative cytology. With successful treatment, their levels (both CSF and serum GRP levels) decrease drastically [32].

4.5.2 CSF - carcino embryogenic antigen

Carcinoembryonic antigen (CEA) is a 180 kd glycoprotein produced by normal intestinal epithelium and glands (sweat and sebaceous) [33,34]. High concentrations of CEA are associated with malignancies of stomach, colon, rectum, and breast, which often correlate with metastatic activity [35,36].

In CM, CSF-CEA can be used in diagnosing and for monitoring the therapy. Its concentration is as high as > 70 ng/ml in CM patients [37]. Jorda *et al* combined traditional CSF cytology used in diagnosing CM with IHC of CSF-CEA and CSF-Epithelial Membrane Antigen (EMA), a glycoprotein found in various cancers like breast, lung, and colon [38]. Their focus was to find out whether IHC tests using CEA and EMA would help to identify CM in cases where cytology is negative or inconclusive with atypical cells. They correlated their findings with either autopsy findings or clinical follow up. Around 52% of cases who developed CM at the end of the study were positive for CEA, and 86% were positive for EMA while 35% were positive for both. Interestingly, in cases with inconclusive cytology results, 75% were positive for CEA, 75% were positive for EMA, and 50% were positive for both while 88% developed CM on follow up. We may

conclude that in patients with lung and breast cancer IHC combined with CEA and EMA can help in predicting and diagnosing CM [39].

CYFRA 21 is a cytokeratin-19 fragment used as a tumor marker in certain lung cancers [40]. CSF-CEA and CSF-CYFRA 21-1 can be used in screening for detecting early CM in lung cancers [41]. Neuron-specific enolase (NSE) is a cell-specific glycolytic enzyme known to be elevated in brain injury as well as certain neuroendocrine tumors, small cell and non-small cell lung cancers [42]. High levels of CSF-CEA, CSF-NSE and CSF-CYFRA 21-1 can be used in the diagnosis of CM when cytology and imaging is inconclusive [41].

4.5.3 CSF – Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), is a signal peptide with a mitogenic property specific for endothelial cells. This factor increases the membrane permeability and helps in vasculogenesis (denovo synthesis of new blood vessels) and angiogenesis (production of new blood vessels from pre-existing blood vessels). They are normally found in lung, kidney, adrenal gland, heart, liver, and stomach mucosa. It has been widely established that VEGF promotes angiogenesis in tumor tissues, and hence, their levels are high in several cancers [43].

Stockhammer et al. compared CSF-VEGF and serum VEGF in patients with CM secondary to solid tumors with those of patients with brain metastasis without CM, meningitis (viral and bacterial), paraneoplastic syndromes and with those with noninfectious and non-neoplastic neurological conditions. They found extremely high levels of CSF-VEGF (> 50 fold) in patients with CM when compared to CSF-VEGF of patients with other conditions while serum VEGF levels were similar in all groups. In bacterial meningitis, CSF – VEGF is high but not as high as in CM, and it is undetectable in brain metastasis without CM and non-neoplastic/noninfectious neurological conditions. CSF- VEGF levels fell drastically after initiation of chemotherapy in CM patients. This study also showed no correlation between CSF – VEGF levels and CSF protein, cell count, and glucose levels; thus making CSF-VEGF an independent diagnostic and prognostic marker in CM, which can be used in addition to already available options to increase detection of CM and monitoring its treatment. Furthermore, VEGF index [Biomarker index = (biomarker CSF/biomarker serum)/(albumin CSF/albumin serum)] is a poor biological marker as it is similar in all groups [44-46].

CSF VEGF levels have potential biomarker role in high-risk cancer patients as elevated. It is considered sensitive and highly specific for the diagnosis of CM from a breast, lung cancer and melanoma [47].

4.5.4 CSF – Urokinase plasminogen activator

Urokinase plasminogen activator (uPA) is a serine protease that is part of an uPA system, which is composed of a receptor (uPAR) and inhibitors, plasminogen activator inhibitor-1 (PAI-1) and PAI-2. This uPA system's role in metastasis by aiding cell proliferation, motility of tumor cells, and adhesion at the secondary site is well established [48]. Overexpression of uPA was associated with worse prognosis in certain malignancies, like gliomas [49]. Its level was found to be higher in patients with CM, but there was no correlation between its levels and survival of patients [46].

4.5.5 CSF – Tissue plasminogen activator

Tissue plasminogen activator (tPA) is a metalloproteinase that increases conversion of plasminogen to active its component, plasmin, which in turn breaks down blood clots. It also augments the cells motility, which is one of the key steps of metastasis [50]. The CSF-tPA concentration in CM is similar to that in other neurological conditions like brain metastasis without CM and meningitis and it cannot be used for diagnosing CM but interestingly the tPA index which is low in CM significantly differs from other conditions and hence when it is combined with other markers, more number of CM can be diagnosed [45].

4.5.6 CSF – Matrix metallo proteinases

Matrix metalloprotineases (MMPs) refer to a group of calcium and zinc based endopeptides that are involved in the destruction of extracellular matrix and help in cell differentiation, apoptosis, and vasculogenesis. In normal individuals, they are highly regulated; however, in malignancy, tumor cells produce high quantities of MMPs, which play a major role in metastasis and tumor growth. Aggressive brain tumors (both primary and metastatic) are

often associated with high activity of gelatinases, a subset of MMPs [51-54].

Profiling CSF- MMPs not only helps in diagnosing CM but also assists in distinguishing patients with CM from those with brain tumors (primary and metastatic) without concomitant CM and normal patients. They are two main gelatinases, gelatinase A (MMP9) and gelatinase B (MMP2) which if in inactive form are known as precursor gelatinase A (pMMP9) and precursor gelatinase B (pMMP2). Other kinds of gelatinase include 130 kDa gelatinase (complex of gelatinase B and TIMP1) and 250kDa gelatinase (a derivative of gelatinase B).

Activated MMP2 is a specific marker for CM and its presence distinguishes it from brain tumors without CM. Even patients with cytology-negative CM (diagnosis made on the basis of imaging and clinical features) have positive MMP2. In brain tumors, pMMP9, pMMP2 and 250kDa activity is seen while pMMP2 is present in normal patients along with those with CM and brain tumors [54].

4.5.7 CSF - Cathepsins

Cathepsins are cysteine proteases. Cathepsin B, cathepsin H, and cystatin C can be used as diagnostic markers in CM. The activity of cathepsin B is higher in colorectal cancers melanoma, and inflammatory neurological diseases, like Guillain–Barré syndrome and multiple sclerosis (MS). Conversely, the activity of cathepsin H is high in melanoma but low in head and neck cancers and inflammatory neurological diseases. Cystatin C is an inhibitor of cysteine proteases, and they are concomitantly low in conditions where cathepsins are high [55-57]. In CM, there is high activity level cathepsins B and cathepsins H in CSF, while cystatin C concentrations are low. Calculation of enzyme activity (cathepsin B or H) to cystatin C concentration can also be used in diagnosing CM [58].

4.5.8 CSF – Glucosephosphate isomerase

Even in the presence of oxygen, rapidly proliferating cancer cells produce the majority of energy by anaerobic glycolysis in which they convert glucose to lactate. Activation of oncogenes, loss of tumor suppressor genes, and hypoxic microenvironment in malignant cells are all factors that might cause such upregulation of glycolysis. Glucosephosphate isomerase (GPI), also known as phosphohexoisomerase is an enzyme needed for the second step of glycolysis where glucose -6-phosphate is converted to fructose-6-phosphate [59,60].

CSF-GPI is high (>20 U/l) in patients with CM. Even though it is not very sensitive (55%), it has reliable specificity (92%), making it a useful diagnostic marker in diagnosing early CM cases, especially when cytology is negative [61].

4.5.9 CSF - Epidermal growth factor receptor

Epidermal Growth Factor Receptor (EGFR) belongs to a group of tyrosine kinase receptors involved in cell proliferation and differentiation through series of signal transduction pathways [62]. In certain malignancies like non-small cell carcinoma, they are known to be overexpressed which led to the development of several anti-EGFR therapies [63].

Mutations in EGFR have gained interest in recent years as they were having an impact on the success of therapy especially the EGFR-tyrosine kinase inhibitors (TKI) in treating NSC lung cancers. Studies show that cancers with activating mutations in tyrosine kinase domain like a mutation in exon 21 responded more than those with deletion of exon 19 [64]. Similarly, patients with CM secondary to NSC lung cancers with favorable EGFR mutations were found in response to EGFR-TKI than those without and hence have a better prognosis [65]. Interestingly tumors having T790M mutation are known to acquire resistance to EGFR TKIs few months into the therapy, making identification of mutations associated with EGFR important before starting therapy [66].

5. OTHER MARKERS

Beta-glucuronidase, LDH, and β2-microglobulin are normal constituents of CSF in low concentrations and are elevated in the central nervous system related infections, malignancies (both primary and metastatic) and CM [67-72]. When used alone, Beta-glucuronidase is a good biomarker with reliable sensitivity and specificity for diagnosing CM but is elevated in conditions like chronic meningitis and is often combined with other markers like CEA, which is not elevated in meningitis, or LDH for more accurate results. B2-microglobulin has a sensitivity of just around 60% and is more specific with hematological cancers [73,74]. Serial measurement of tumor markers like CA-15.3, CA-125 and CA-19.9 help in monitoring

disease progression and response to treatment [75,76].

CSF – prostate specific antigen (PSA) in prostate cancer, cytology negative patient [77]. We determined the concentration of VEGF, tPA, uPA, and TGF $[beta]_1$ in CSF and serum of tumor patients with proven LM or without LM and in patients with bacterial or viral meningitis to study their value as biomarkers for LM [46,78].

6. FISH

Fluorescence in situ hybridization (FISH), wherein specific DNA or RNA probes are used in to identify numerous chromosomal abnormalities, is often used cytological techniques used in diagnosing cancers and genetic diseases. It has 100 % specificity and good sensitivity (83%) [79]. In patients with high suspicion of CM and inconclusive CSF-cytology, FISH can be used. It not only increases the diagnostic yield and help to catch CM in early stages but also saves patients from repeated lumbar puncture and multiple other tests if their first cytology tests are inconclusive [80,81].

7. CIRCULATING TUMOR CELLS

Circulating tumor cells (CTC) refer to tumor cells that break away from the primary tumor found in blood and CSF. It is known to be a useful biomarker for tracking metastasis, disease progression and response to treatment [82-84]. Rare cell capture technology (RCCT) is used in identifying these CTCs efficiently. It has 100% sensitivity and 97.2% specificity. This technology is much better than conventional cytology with a sensitivity of 66% or MRI with a sensitivity of 73% or combination of both which has a sensitivity of 86% can be utilized in the early diagnosis of CM [85]. PCR and tumor marker-immunostaining fluorescence *in situ* hybridization with appropriate enrichment medium and technology can increase the yield of detecting CTCs (TM-iFISH) [86,87].

8. CSF DERIVED CIRCULATING TUMOR DNA (CTDNA)

Characterization of ctDNA offers an ultrasensitive and non-invasive approach to personalized and predictive medicine [88], CtDNA has been demonstrated in CSF of patients with brain tumors (8,9). Genomic characteristics of the primary tumor and its metastases show considerable intra-patient and even intra-tumor heterogeneity. Thus, the current standard of practice, analysis of the diagnostic specimen alone, may fail to capture the real-time cancer profile during therapy. Patients with brain tumors do not present with or present with low amounts of ctDNA in plasma 83precluding the genomic characterization of brain cancer through plasma ctDNA. ctDNA derived from central nervous system tumors is more abundantly present in the cerebrospinal fluid (CSF) than in plasma. CSF ctDNA has shown to complement the diagnosis of leptomeningeal carcinomatosis.

The CtDNA present in the CSF has been compared with plasma CtDNA by sequencing DNA obtained from tumor samples, plasma, and CSF of a cohort of 12 patients. It was demonstrated that ctDNA from CSF was relatively more representative and higher sensitivity of brain tumor genomic alterations than ctDNA from plasma. Next generation sequencing of CSF CtDNA has well characterized the genomic alterations of brain tumors than plasma, allowing the identification of actionable brain tumor somatic mutations. Parallel sequencing of CSF CtDNA also characterized actionable brain tumor somatic mutations and copy number alterations of EGFR, PTEN, ESR1, IDH1, ERBB2, and FGFR2, CSF CtDNA also has a potential as an excellent biomarker by serial assessment of CSF ctDNA levels to assess the therapeutic response and to monitor tumor progression.

9. PREDICTORS OF PROGNOSIS

Response to therapy after 6 weeks of therapy is best (80%) in patients with positive cytology and negative MRI findings while those with both positive cytology and MRI findings was worst (29%). Intermediate response (55%) was seen in patients with negative cytology and positive MRI findings. Interestingly overall survival was similar in all categories [7].

At diagnosis, females with longer duration of symptoms but without elevated CSF proteins and cerebral leptomeningeal clinical involvement and those treated with intrathecal chemotherapy are found have a better prognosis [89,90]. Serial measurement of CSF biomarkers and cytology can help in tracking disease progression and response to therapy. Any improvement in marker's levels and disappearance of malignant cells favor good prognosis [25].

Table 1. CSF - Tumor markers for various cancers [8,23,30,35,36,44-47,49,54,58,77,91-100]

Organs involved	Biomarkers
Breast	β2- Glucorinidase
	β2 microglobulin
	CEA + EMA
	LDH
	VEGF
	IL-8 (CXCL-8)
	PARC (CCL18)
	IP-10 (CXCL10)
	CXCL 12
	SDF-1
	CA 15.5
	CA 125
	CA 19.9
	HER-2
Lung	β 2 glucorinidase
	CEA + EMA
	LDH
	VEGF
	uPA
	EFGR
	GRP (SCLC)
	CYFRA 21
	NSE (SCLC, NSCLC)
	IL-8 (CXCL-8)
	PARC (CCL18)
	IP-10 (CXCL10)
	MMP2 (SCLC)
	MMP9 (SCLC)
	Cathespin B
	H-cystatin
	SDF-1
	CA 15.5
	CA 125
	CA 19.9
	HER-2
Colon	CEA + EMA
	IL-8 (CXCL-8)
	PARC (CCL18)
	IP-10 (CXCL10)
	Cathespin B
	H-cystatin
	CA 15.5
	CA 125
	CA 19.9
Ovarian	VEGF
	uPA
	IL-8 (CXCL-8)
	PARC (CCL18)
	IP-10 (CXCL10)
	HER-2
Lymphoma (NHL)	VEGF
	LDH
	uPA
	IL-8 (CXCL-8)

Organs involved	Biomarkers
	PARC (CCL18)
	IP-10 (CXCL10)
	Anti-thrombin III
Melanoma	LDH
	VEGF
	tPA
	uPA
	IL-8 (CXCL-8)
	PARC (CCL18)
	IP-10 (CXCL10)
	CXCL-12
	MMP2, MMP9
	SDF-1
	9.2.27
B-cell Non hodgkins lymphoma	CD 20
	CD 52
Chronic lymphoctic leukemia	CD 20
	CD 52
Non-specific markers for solid tumors	Angiogenesis
Glioma	uPA
	IL-13
Prostate	PSA
	Cathespin B
	H-cystatin
Gall bladder cancer	CEA
	CA-199
Unknown cancer	VEGF
	tPA
Cervical cancer	CEA
	VEGF
	CA 15.5
	CA 125
	CA 19.9

VEGF – Vascular Endothelial Growth Factor, SDF – Stromal cell derived factor, CEA Carcino embryonic antigen, CA - , HER – Human Epidermal Growth Factor Receptor, EFGR- Epidermal growth factor receptor, IP - Interferon-gamma inducible protein, PARC - Pulmonary and Activation Regulated Chemokine, IL – Interleukin, MMP – Matrix metalloproteinases, SCLC- squamous cell lung cancer, tPA - Tissue plasminogen activator, uPA - Urokinase plasminogen activator , SDF- stromal cell-derived factor

10. CONCLUSION

With improving overall survival of cancer patients, the incidence of CM is expected to further rise in future. Customary methods (CSF cytology and imaging) have limitations given there unreliable sensitivity and specificity. This calls for more reliable methods for early detection of CM, and biomarkers can have a major role when combined with CSF cytology and imaging modalities. In conclusion, the management of the meningeal carcinomatosis is individualized considering comprehensive evaluation of tumor burden, cytological, neuroimaging and molecular profiling in the cerebrospinal fluid. However, the definitive role of these modalities in combination needs further validation in larger cohorts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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