14 Clinical, Imaging, and CSF Cytological Presentation of Leptomeningeal Metastases from Solid Non-CNS Primary Tumors

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14.1 Introduction

Leptomeningeal metastasis (LM) is defined as the spread of malignant cells in the subarachnoid space and in the leptomeninges. It is sometimes denoted as carcinomatous meningitis, in case of carcinoma, or neoplastic meningitis, but this term is misleading since it suggests a disorder that is primarily of inflammatory origin. LM may be observed in approximately 10% of patients with metastatic cancer [1].

The risk of experiencing LM in the course of systemic cancer today is probably higher than that figure, given that patients survive much longer, that diagnostic approaches have changed dramatically with the introduction of magnetic resonance imaging (MRI) and advanced cytology and even liquid biopsy techniques to detect cancer cells in the cerebrospinal fluid (CSF), and that the cerebrospinal compartment may be more difficult to control using systemic therapies than other body compartments. In up to 70%, the diagnosis of LM is made in the context of systemic disease progression. Breast cancer, lung cancer and melanoma are the three main causes of LM.

The median survival is limited to a few months and once neurological signs are present, they are fixed and rarely improved by therapeutic interventions. Thus, the diagnosis should be made as soon as possible in case of suspicion of LM in order to prevent neurological deterioration. The diagnosis is based on clinical evaluation, cerebrospinal MRI and CSF analysis [2].

14.2 Risk Factors

Risk factors for LM include an opening of the ventricular system during brain metastasis surgery, resection of cerebellar metastases especially when using a piece-meal resection [3–8] and primary tumor-related factors. In breast cancer patients, lobular subtype and triple negative status (absence of estrogen receptors, absence of progesterone receptors, absence of HER2 expres-

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sion) have been reported as risk factors of LM [9]. HER2 overexpression alone has been shown to be a risk factor of brain metastases; however, its role as a risk factor of LM is less clear. In lung cancer patients, EGFR mutation has been reported as being a risk factor of LM in a large retrospective cohort of 5387 non-small-cell lung (NSCLC) patients, where 184 cases of LM were identified [10]. The role of other driver mutations for LM risk has not been defined.

Only limited data are available on melanoma LM patients, and no risk factor has been identified.

14.3 Clinical Presentation

Symptoms and signs depend on the neuroanatomical regions involved by LM and are often multifocal. Headache, nausea and vomiting, mental changes, gait difficulties, cranial nerve palsies, sensori-motor deficits, cauda equina syndrome, and radicular and back pain, depending on the distribution of tumor cells in the CNS, are considered typical signs of LM [2]. The clinical presentation can be subtle with discrete and isolated symptoms and signs. Thus, a detailed clinical evaluation is required at diagnosis and during follow-up. Symptoms and signs of LM should be differentiated from those related to concomitant brain metastases and neurological complications of the cancer and its treatment. A standardized scorecard has been proposed by the RANO group [11], but it has not been validated yet.

14.4 Radiological Presentation

LM may be a diffuse disease of the entire central nervous system and cerebrospinal imaging is thus required for the staging of LM [2, 12]. Cranial computed tomography (CT) should be performed only in patients with contraindications to MRI and has its limitations in particular for the assessment of the spinal cord. The radiologic assessment of LM can be challenging. Some technical aspects should be considered when evaluating LM patients, such as slice positioning and slice thickness, and time interval between injection of contrast agent and acquisition of images. Contrast agent should be injected 10 min before image acquisition and the slice thickness should be 1 mm or less in the brain and 3 mm or less for the spinal cord [2]. Lumbar punctures should be performed after MRI since they may induce a meningeal enhancement. The most sensitive sequence for the detection of LM is the contrast-enhanced T1-weighted sequence [13, 14]. The follow-up should be performed on the same device or on an MRI scanner with identical field strength.

Typical MRI findings include linear or nodular leptomeningeal enhancement on the leptomeninges. These findings can be observed at sulcal, ependymal, cranial nerve or cauda equina levels. Communicating hydrocephalus can also be observed in LM because of poor CSF resorption. Differential diagnosis includes focal dural enhancement after surgery, pachymeningitis, meningioma en plaque, brain metastases, CNS vasculitis, Moyamoya disease, neuro-sarcoidosis, and various inflammatory and infectious diseases.

A scorecard to rate neuroimaging findings in LM has been proposed by the RANO group, but this has not been validated and is therefore currently under revision.

The radiological presentation of LM help to guide clinical decision making. Four subtypes have been delineated in the EANO ESMO guidelines [2]: A, diffuse linear leptomeningeal disease, B nodular leptomeningeal disease, C a combination of A and B, and D no focal lesions, but potentially hydrocephalus (see Table 14.1).

Parenchymal brain metastases are associated with LM in 31–66% of patients with breast cancer [15–23], 56–82% of patients with lung cancer [24–30] and 57–87% of patients with melanoma [31–33].

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) is not helpful for the diagnosis or follow-up of LM. CSF flow studies using ^{111}indium-DTPA or ^{99}technetium macroaggregated albumin have been recommended in candidates for intra-CSF pharmacotherapy if CSF flow blocks are suspected.

Table 14.1 EANO ESMO classification of LM (based on Le Rhun et al., 2017) [2]

		Cytology/ biopsy	MRI	Confirmed	Probable[a]	Possible[a]	Lack of evidence
Type I: positive CSF cytology or biopsy	IA	+	Linear	+	n.a.	n.a.	n.a.
	IB	+	Nodular	+	n.a.	n.a.	n.a.
	IC	+	Linear + nodular	+	n.a.	n.a.	n.a.
	ID	+	Normal	+	n.a.	n.a.	n.a.
Type II: clinical findings and neuroimaging only	IIA	− or equivocal	Linear	n.a.[b]	With typical clinical signs	Without typical clinical signs	n.a.
	IIB	− or equivocal	Nodular	n.a.	With typical clinical signs	Without typical clinical signs	n.a.
	IIC	− or equivocal	Linear + nodular	n.a.	With typical clinical signs	Without typical clinical signs	n.a.
	IID	− or equivocal	Normal	n.a.	n.a.	With typical clinical signs	Without typical clinical signs

[a]Requires a history of cancer
[b]Not applicable

14.5 CSF Cytology

Indirect, but non-diagnostic pathological findings are frequently observed in the CSF of LM patients. An increased opening pressure (>200 mm H_2O) is noted in 21–42% [28, 34], high protein levels (>50 mg/dL) in 56–91% [16, 21, 28, 34, 35], decreased glucose levels (<60 mg/dL) in 22–63% [21, 28, 34, 35] and increased leukocyte counts (>4/mm^3) in 48–77.5% of the patients [21, 28, 34, 35].

CSF standard cytology is the gold standard to confirm the diagnosis of LM. The identification of malignant cells in the CSF during standard CSF cytology confirms the diagnosis of LM. The CSF should be considered as negative only in the unequivocal absence of tumor cells. In the presence of suspicious or atypical cells, the CSF should be reported as equivocal.

The sensitivity of standard cytology is moderate to low. Simple measures should be taken to facilitate the detection of malignant cells in the CSF, such as obtaining at least 5 mL of CSF, ideally more than 10 mL, processing the CSF within 30 minutes after sampling and avoiding blood contamination of the CSF [2, 11, 36–38]. If the first CSF cytology is negative or equivocal, a second sample should be obtained which reportedly increases the sensitivity to 80%. The usefulness of further CSF samples remains unclear. CSF fixation in dedicated tubes has been shown to increase the diagnostic yield in hematological diseases, but the usefulness of this approach remains to be established for solid tumors [39].

Novel technologies using epithelial cell adhesion molecule (Ep-CAM) antibodies or other tumor-specific antibody-covered magnetic nanoparticles such as high-molecular weight-melanoma-associated antigen/melanoma-associated chondroitin sulfate proteoglycan (HMW-MAA/MCSP) can identify circulating tumor cells and should contribute in the future to a higher sensitivity of detecting malignant cells in the CSF.

The Veridex Cellsearch® assay has been approved by FDA for the detection of tumor cells in peripheral blood [40]. Different adaptations of the technique have been developed for

the detection and quantification of tumor cells in the CSF [41–46], but no standard has been established until now. Tumor cells can be identified using flow cytometry with fluorescently labelled antibodies against membrane-bound proteins of tumor cells coupled with fluorescence-activated cell sorting (FACS) for the quantification of tumor cells [47, 48].

Cell-free circulating tumor DNA (ctDNA) represents a fraction of total cell-free DNA originating from necrotic and apoptotic cells. Genomic alterations can be detected by micro-arrays [49], digital/real-time polymerase chain reaction (RT-PCR), targeted amplicon sequencing and whole exome sequencing [50–53]. Analysis of ctDNA in the CSF may help the diagnosis when the standard CSF cytology is negative, detect actionable genomic targets and monitor the response to treatment [54]. CSF ctDNA is probably more sensitive than CSF standard cytology for the detection of LM [55]. However, the detection of ctDNA in the CSF may be caused by concomitant brain parenchymal metastases or by blood contamination during CSF sampling and should be interpreted cautiously for the diagnosis and follow-up of LM [2]. In NSCLC, the determination of EGFR and T790M status at LM diagnosis and during the follow-up can help to guide the therapeutic strategy. Promising results were observed after treatment with osimertinib, an oral third-generation EGFR tyrosine kinase inhibitor that is active in tumors expressing the EGFR T790M resistance mutation [56]. DNA methylation profiling in the CSF represents another promising tool for the diagnosis and the management of LM [57] .

14.6 Diagnosis of LM

According to EANO ESMO guidelines, the diagnosis of LM can be either confirmed, in the presence of tumor cells in the CSF, or probable, or possible, or there may be lack of evidence [2] (see Table 14.1). Two major criteria define the LM classification: (1) the confirmation of the diagnosis by CSF cytology (confirmed LM, type I) versus not confirmed (type II), and (2) the MRI presentation: linear disease for type A, nodular disease for type B, a combination of both linear and nodular disease for type C and no neuroimaging evidence of LM except hydrocephalus for type D. This classification aims at guiding the therapeutic strategy and requires confirmation in prospective studies.

14.7 Conclusion

The diagnosis of LM is based on clinical manifestation, cerebrospinal MRI findings and standard CSF cytology and is often challenging. Standardized scorecards should be used for the clinical and imaging follow-up of patients; however, no such scorecard has been validated yet. Characterization of genomic alterations and methylation profiles may improve the sensitivity of CSF analysis in the future.

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