Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: http://scholarsmepub.com/

Carcinomatous Meningitis from Solid Tumors: A Seven Years' Experience in Moroccan Patients

Maha Ait Berri[1*], Aziz Bazine[2], Abdellah Taous[1], Tarik Boulahri[1], Imane Traibi[1], Mohamed Fetohi[2], Abdelhadi Rouimi[1]
[1]Department of Neurology, Military Hospital Moulay Ismail, Meknes, Morocco
[2]Department of Medical Oncology, Military Hospital Moulay Ismail, Meknes, Morocco

Original Research Article

***Corresponding author**
Maha Ait Berri

Article History
Received: 22.02.2018
Accepted: 10.03.2018
Published: 30.03.2018

DOI:
10.21276/sjmps.2018.4.3.12

Abstract: Carcinomatous meningitis from solid tumors has not been investigated in detail in the Moroccan population. Therefore, we reviewed our experience with this disease to determine its clinical features and treatment outcomes in Moroccan patients. We performed a retrospective review of all patients with solid cancers admitted to the Military Hospital Moulay Ismail in Meknes, Morocco with carcinomatous meningitis between January 2011 and December 2017. A total of 12 patients were included. 5 were males and 7 were females. The median age was 54 years old (39 – 77 years old). The most frequent primary tumor was breast cancer (50%) and lung cancer (34%). The median time from initial cancer diagnosis to the development of carcinomatous meningitis was 6.9 months (0 – 49 months). The most common symptoms were headache (67%), nausea and vomiting (42%), and vision changes (34%). The diagnosis of CM was established by both CSF cytology and MRI in 25% of patients, by CSF cytology alone in 17%, and by MRI alone in 58%. One of the 12 patients received supportive care only. Chemotherapy was the only treatment for 50% of patients, 17% received radiotherapy alone, and 25% received both chemotherapy and radiotherapy. The median survival from the time of carcinomatous meningitis diagnosis was 9 weeks (2 – 29 weeks). Our results confirm the continued poor prognosis of carcinomatous meningitis in Moroccan patients with solid tumors as well. Further clinical trials are needed to improve therapeutic strategies including prophylactic approaches.
Keywords: Carcinomatous meningitis; Solid tumors, Diagnosis, Therapeutics, Survival.

INTRODUCTION

The term carcinomatous meningitis (CM), also known as leptomeningeal metastasis or neoplastic meningitis, is a rare neurological disorder caused by the spread of tumor cells to leptomeninges (pia and arachnoid) and subarachnoid space, and their dissemination through the cerebrospinal fluid (CSF) [1-3]. It was first described by Eberth in 1870 [4,5].The incidence of CM typically varies by primary tumor type, occurring in approximately 5% to 8% of patients with solid tumors [1]. Adenocarcinoma is the most frequent histology and breast, lung, and melanoma are the most common primary sites to metastasize to the leptomeninges. Although small cell lung cancer and melanoma have the highest rates of spread to the leptomeninges (11% and 20%, respectively), due to the higher incidence of breast cancer, the latter accounts for most cases in large series of the disorder [6]. According to guidelines published by the National Comprehensive Cancer Network (NCCN) [7], the diagnosis of CM may be determined by the presence of circulating tumor cells (CTCs) in the CSF. In the absence of CTCs in the CSF, CM has been defined as the presence of neuroradiological findings consistent with CM and associated with characteristic symptoms and signs of CM in the setting of cancer. A diagnosis of probable CM can also be made in those with cancer who present with symptoms and signs consistent with CM, CSF abnormalities (although nonspecific), and inconclusive findings on magnetic resonance imaging (MRI) [8]. The therapeutic spectrum includes radiotherapy of the clinically involved region as well as systemic and intrathecal chemotherapy [9].

To the best of our knowledge, the clinical and therapeutic characteristics of CM from solid tumors have not been investigated in detail in the Moroccan population. In the present retrospective study, we reviewed our experience with this disease to determine its clinical features and treatment outcomes in Moroccan patients.

MATERIALS AND METHODS

We performed a retrospective review of all patients with solid cancers admitted to the Military

Hospital Moulay Ismail in Meknes, Morocco with CM between January 2011 and December 2017.

Data on these patients were drawn from the medical records, including age, sex, date of initial cancer diagnosis, date of CM diagnosis, site, histology and extension of primary cancer, neurological symptoms and signs, performance status according to Karnofsky at CM diagnosis, MRI and CSF results, treatment for CM and date of death or last follow-up.

Statistical analysis was performed using Epi Info version 7.2. Categorical data were presented as numbers with percentages, while continuous data were presented as means and standard deviations or medians with extreme values. Overall survival was defined as the time from CM diagnosis to the time of death or last follow-up.

The Local Review Board of the Military Hospital Moulay Ismail in Meknes, Morocco approved this retrospective study and waived the requirement for informed consent because of the use of de-identified data.

RESULTS

A total of 12 patients were included in this study. 5 were males and 7 were females. The median age at diagnosis of CM was 54 years old (39 – 77 years old). The most frequent primary tumor in our study was breast cancer (50%), followed by lung cancer (34%), gastric cancer (8%) and melanoma (8%). Only 25% of patients had localized disease at the time of initial primary diagnosis and 75% metastatic disease. CM was the first manifestation of cancer in 17% of patients. The median time from initial cancer diagnosis to the development of CM was 6.9 months (0 – 49 months) (Table 1).

The most common symptom among patients with CM were headache (67%), nausea and vomiting (42%), vision changes (34%), gait disturbance (25%), cranial nerve palsy(25%), lower extremity weakness(25%), confusion (8%) and seizure (8%). Physical examination revealed the presence of neck stiffness in 25 % of patients. The median performance status according to Karnofsky at CM diagnosis was 60 (20 – 100). The diagnosis of CM was established by both CSF cytology and MRI in 25% of patients, by CSF cytology alone in 17%, and by MRI alone in 58% (Table 2).

One of the 12 patients with CM received supportive care and symptomatic treatment only. Chemotherapy was the only treatment for 50% of patients, 17% received radiotherapy alone, and 25% received both chemotherapy and radiotherapy. A total of 9 patients received chemotherapy: systemic chemotherapy alone in 45%, intrathecal methotrexate alone in 22% and both in 33%. Radiotherapy was given to 5 patients: focal radiation in 20%, whole brain radiation in 60%, and combined in 20% (Table 3). The median survival from the time of CM diagnosis was 9 weeks (2 – 29 weeks).

Table-1: Demographic data and primary tumor characteristics of CM patients

Characteristic	Number of patients	Percentage
Total of patients	*12*	*100%*
Age (years)		
Median	54	
Range	39 – 77	
Sex		
Male	5	42%
Female	7	58%
Site and histology of primary tumor		
Breast cancer	6	50%
Lung cancer		
NSCLC	2	17%
SCLC	2	17%
Gastric cancer	1	8%
Melanoma	1	8%
Extension of primary tumor at initial diagnosis		
Localized disease	3	25%
Metastatic disease	9	75%
Interval from diagnosis of primary tumor to diagnosis of CM (months)		
Median	6.9	
Range	0 – 49	
Abbreviations: CM = carcinomatous meningitis; NSCLC = non-small cell lung cancer; NSCLC = small cell lung cancer.		

Table-2: Neurological presentations, KPS and diagnosis of CM patients

Characteristic	Number of patients	Percentage
Symptoms and signs		
Headache	8	67%
Nausea and vomiting	5	42%
Vision changes	4	43%
Gait disturbance	3	25%
Cranial nerve palsy	3	25%
Lower extremity weakness	3	25%
Confusion	1	8%
Seizure	1	8%
Neck stiffness	3	25%
KPS		
Median	60	
Range	20 – 100	
Diagnosis		
CSF cytology (+), MRI (+)	3	25%
CSF cytology (+), MRI (–)	2	17%
CSF cytology (–), MRI (+)	7	58%
Abbreviations: CM = carcinomatous meningitis; KPS = Karnofsky performance status; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.		

Table-3: Treatment modalities of CM patients

Modality	Number of patients	Percentage
BSC	*1*	*8%*
CT alone	*6*	*50%*
RT + CT	*3*	*25%*
RT alone	*2*	*17%*
CT	*9*	*75%*
Intrathecal MTX	2/9	22%
Systemic CT	4/9	45%
Intrathecal MTX + systemic CMT	3/9	33%
RT	*5*	*42%*
Focal RT	1/5	20%
WBRT	3/5	60%
Focal RT + WBRT	1/5	20%
Abbreviations: CM = carcinomatous meningitis; BSC = best supportive care; CT = chemotherapy; RT = radiotherapy; MTX = Methotrexate; WBRT= whole-brain radiotherapy.		

Table-4: Symptoms and signs of carcinomatous meningitis [1]

Brain	Spine	Clinical syndromes

• Headache
• Nausea/vomiting
• Confusion
• Cranial nerve palsies
  ▪ *Vision changes (particularly double vision)*
  ▪ *Facial numbness, weakness*
  ▪ *Tinnitus, decreased hearing*
  ▪ *Dysphagia*
  ▪ *Dysarthria*
• Ataxia
• Cognitive impairment
• Seizure
	• Bowel/bladder dysfunction
	• Paresthesias
	• Pain (neck, back, or radicular)
	• Focal weakness
	• Hyporeflexia
	• Neck stiffness
		• Rapidly progressive dementia
		• Syndrome of inappropriate diuretic hormone secretion (SIADH)
		• Multiple cranial neuropathies

Table-5: Differential diagnoses of carcinomatous meningitis [1,2,21]

- Infectious meningitis
  - Bacterial: *Listeria monocytogenes, Neisseria meningitidis, Mycobacterium tuberculosis, Haemophilus influenzae, Borrelia burgdorferi, Streptococcus pneumonia or agalactiae*
  - Fungal: *Cytomegalovirus, Epstein-Barr virus, Varicella zoster virus, Herpes simplex virus, JC virus, Paramyxovirus, Morbillivirus, Arbovirus, Human immunodeficiency virus*
  - Viral: *Candida, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioidies, Blastomyces*
- Multiple brain metastases
- Chemical meningitis/arachnoiditis (secondary to intrathecal chemotherapy)
- Paraneoplastic syndrome
  - *Paraneoplastic cerebellar degeneration*
  - *Encephalomyelitis*
  - *Limbic encephalitis*
- Intracranial hypotension (secondary to lumbar puncture)
- Metabolic or chemotherapy-induced neuropathy
- Toxic metabolic encephalopathy
- Cord compression
- Steroid myopathy
- Neurosarcoidosis

Table-6: Treatment recommendations for CM [9]

Type of CM								
Diagnosis by gd-MRI	*Nodular-solid type*				*Diffuse non-adherent type*			
Parenchymal brain metastasis?	*Yes*		*No*		*Yes*		*No*	
Systemic disease/metastasis present?	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
Intrathecal CT					+	+	+	+
Systemic CT	+	+	+		+		+	
Focal RT	+	+	+	+	+	+		
WBRT	+	+	+	+	+	+		

Abbreviations: CM = carcinomatous meningitis; CT = chemotherapy; RT = radiotherapy; WBRT= whole-brain radiotherapy.

DISCUSSION

CM is the third most common cause of central nervous system metastases after brain metastases and epidural spinal cord compression [8]. Primary tumors more frequently associated with cases diagnosed with CM are breast, lung and melanoma carcinomas [1, 5, 10]. In our series, lung and breast adenocarcinoma were also the most common primary sites, accounting for 84% of all cases. Melanoma, which was found in only one patient in our study, may reflect the low incidence of this condition in Morocco. The present study also included one case of gastric cancer, which was rarely reported to have caused CM [11–13]. In more than 70% of patients CM develops in the setting of an active systemic disease, in 20% of patients it occurs in association with a stable disease, and in only 5 to 10% of patients it is the first manifestation of cancer [2,14,15], while 17% of our patients presented with CM at the time of initial primary diagnosis. The median time from initial cancer diagnosis to the development of CM in the present study was 6.9 months, shorter than that reported by other authors (12 – 18 months) [16–18], probably because the majority of our patients (75%) presented with metastatic disease at initial primary diagnosis.

Symptoms of CM result from multiple interrelated events: obstruction of CSF reflux leading to hydrocephalus, direct compression of parenchyma, ischemia secondary to vessel involvement, metabolic strain, parenchymal invasion and disruption of the blood-brain barrier [19–21]. Common clinical findings are often attributable to spinal and cranial nerve dysfunction, meningeal irritation, or increased intracranial pressure (Table 4) [1].

The development of such neurological signs and symptoms in a patient with known metastatic cancer is highly suspicious for CM [21, 22]. Nevertheless, it remains important to rule out alternative causes, such as parenchymal disease, chemotherapy or radiation side effects, paraneoplastic syndromes, infectious etiologies, or sarcoidosis (Table 5) [1,2,21].

Consistent with previous studies [18, 23–25], cerebral symptoms were the most common presenting symptoms in our series at the time of CM onset. Headache, nausea and vomiting, and changes in vision were present in 67%, 42%, and 34% of overall cases, respectively. Spinal symptoms, such as lower extremity

weakness and neck stiffness, were less common in our study, occurring in only 25% of all cases.

The identification of CTCs by CSF cytology is the gold standard for diagnosis of CM, having a specificity of about 95 %. However, its sensitivity is less than 50 % and depends on how many times the lumbar punctures are repeated [25, 26]. In our series CSF cytology was positive in 42% of patients. This rate of positive cytology was lower than that reported by other authors [18, 27, 28]. Glantz *et al*. reported that the high rate of false negatives in CSF cytology is due in part to the lack of standardized techniques for obtaining and evaluating this procedure and identified four sources of error: obtaining CSF distant from the site of symptoms, insufficient sample volume, delayed processing and acquisition of less than two samples [29].

Brain and spine gadolinium-enhanced magnetic resonance imaging (gd-MRI) is the other gold standard for the diagnosis of CM. Compared to brain computed tomography (CT), gd-MRI is more sensitive for the assessment of CM [25, 30, 31]. Important characteristic findings of CM on gd-MRI include diffuse or focal leptomeningeal enhancement, enhancement of intradural spinal nerves, intradural nodules, and superficial multiple cerebral metastases. The differential diagnosis for meningeal enhancement must be made from infection, inflammation (rheumatoid arthritis), granulomatous infiltration (neurosarcoidosis), subarachnoid hemorrhage, Guillain-Barre syndrome, chemical meningitis, intracranial hypotension, and previous lumbar puncture [19,32]. In our series, gd-MRI was positive in 83% of the cases. This high rate of CM diagnosis by MRI was also reported in previous studies [23, 25, 27].

Because of the paucity of prospective, randomized trials for CM, most treatment recommendations are based on retrospective studies with a low level of evidence and expert opinion (Table 6) [1, 9].

The median survival of patients with non-treated CM is 4 to 6 weeks and death often occurs due to progressive neurologic dysfunction. Treatment is intended to improve neurologic quality of life, and prolong survival. Fixed neurologic symptoms rarely improve with treatment, but the progression of neurologic deterioration may be stopped in some cases and median survival can be increased to 4 – 8 months [2,6]. In our series, the median survival from the time of CM diagnosis was 9 weeks, consistent with previous series [17, 23, 33]. This short survival reflects the poor prognosis of CM in our patients because the most of them (83%) presented at diagnosis of CM with a widely disseminated and progressive systemic cancer and were heavily pretreated with radiotherapy and systemic chemotherapy.

CONCLUSION

Our results confirm the continued poor prognosis of CM in Moroccan patients with solid tumors as well. Prospective studies with larger cohorts are required to establish the possible prognostic factors that would facilitate selecting patients who could benefit from hospice measures only or specific treatments. Further clinical trials are also needed to improve therapeutic strategies of CM from solid tumors including prophylactic approaches.

Competing interests

The authors declare no competing interest.

Authors' contributions

All authors contributed to the work and read and approved the final version of the manuscript.

REFERENCES

1. Wang, N., Bertalan, M. S., & Brastianos , P. K. (2018). Leptomeningeal metastasis from systemic cancer: Review and update on management. Cancer, 124(1): 21-35.
2. Pellerino, A., Bertero, L., Rudà, R., & Soffietti, R. (2018). Neoplastic meningitis in solid tumors: from diagnosis to personalized treatments. Ther Adv Neurol Disord, 11: 1-15.
3. Duan, H., Li, M., & Sun, X. (2014). Clinical features of patients with carcinomatous meningitis in the Chinese population: report of 4 cases and review of the literature. Turk Neurosurg, 24(1): 13-18.
4. Eberth, C. (1870). Zur Entwicklung des Epitheliomas (Cholesteatoms) der Pia und der Lunge. Virchow Arch, 49: 51.
5. Mateos, A. J., Naranjo, F. C., Hernández, A. G., Pi, O. F., Nicolás, S. D., & Fernández, J. L. (2011). Neoplastic meningitis. Review of a clinical series. Neurol Barc Spain, 26(4): 227-232.
6. Chamberlain M. C. Leptomeningeal metastasis. (2010). Semin Neurol, 30(3): 236-244.
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1.2018. Accessed 18 Marsh 2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
8. Le Rhun, E., Taillibert, S., & Chamberlain M. C. (2017). Neoplastic Meningitis Due to Lung, Breast, and Melanoma Metastases. Cancer Control, 24(1): 22-32.
9. Mack, F., Baumert, B. G., Schäfer, N., Hattingen, E., Scheffler, B., Herrlinger, U., & Glas, M. (2016). Therapy of leptomeningeal metastasis in solid tumors. Cancer treatment reviews, 43, 83-91.
10. Le Rhun, E., Weller, M., Brandsma, D., Van den Bent, M., de Azambuja, E., Henriksson, R., & al. (2017). EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours.

Ann Oncol, 28(suppl_4): iv84-iv99.
11. Du, C., Hong, R., Shi, Y., Yu, X., Wang, J. (2013) Leptomeningeal metastasis from solid tumors: a single center experience in Chinese patients. J Neurooncol, 115(2): 285-291.
12. Tomita, H., Yasui, H., Boku, N., Nakasu, Y., Mitsuya, K., Onozawa, Y., & al. (2012). Leptomeningeal carcinomatosis associated with gastric cancer. Int J Clin Oncol, 17(4): 361-366.
13. Oh, S. Y., Lee, S. J., Lee, J., Lee, S., Kim, S. H., Kwon, H. C., & al. (2009). Gastric leptomeningeal carcinomatosis: Multi-center retrospective analysis of 54 cases. World J Gastroenterol WJG, 15(40): 5086-5090.
14. Chamberlain, M. C. (2010). Leptomeningeal metastasis. Curr Opin Oncol, 22(6): 627-635.
15. Gleissner, B., & Chamberlain, M. C. (2006). Neoplastic meningitis. Lancet Neurol, 5(5): 443-452.
16. Waki, F., Ando, M., Takashima, A., Yonemori, K., Nokihara, H., Miyake, M., & al. (2009). Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. J Neurooncol, 93(2): 205-212.
17. Oechsle, K., Lange-Brock, V., Kruell, A., Bokemeyer, C., & de Wit M. (2010). Prognostic factors and treatment options in patients with leptomeningeal metastases of different primary tumors: a retrospective analysis. J Cancer Res Clin Oncol, 136(11): 1729-1735.
18. Hyun, J. W., Jeong, I. H., Joung, A., Cho, H. J., Kim, S. H., & Kim, H. J. (2016). Leptomeningeal metastasis: Clinical experience of 519 cases. Eur J Cancer, 56: 107-114.
19. Martins, S. J., de Azevedo, C. R. A. S., Chinen, L. T. D., Cruz, M. R. S., Peterlevitz M. A., & Gimenes D. L. (2011). Meningeal carcinomatosis in solid tumors. Arq Neuropsiquiatr, 69(6): 973-980.
20. Cui, J. Z., He, J. Y., Li, Q., Li, X. Q., Gao, R. P., Bu, H., Zou ,Y. L., Guo, X. S., Han, W. X., Zhao, Z. Y., Li, Y. Y., Zheng, M. M., Liu, Y. J., & Yan, L. T. (2017). Advancements in diagnosis and treatment of meningeal carcinomatosis in solid cancer. Neuroimmunology and Neuroinflammation, 4:167-178
21. Nayar, G., Ejikeme, T., Chongsathidkiet, P., Elsamadicy, A. A., Blackwell, K. L., Clarke, J. M., & al. (2017). Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget, 8(42):73312-73328.
22. Chamberlain, M. C. Neoplastic meningitis. (2008). The Oncologist, 13(9): 967-977.
23. Clarke, J. L., Perez, H. R., Jacks, L. M., Panageas, K. S., & DeAngelis, L. M. (2010). Leptomeningeal metastases in the MRI era. Neurology, 74(18):1449-1454.
24. Palma, J. A., Fernandez-Torron, R., Esteve-Belloch, P., Fontes-Villalba, A., Hernandez, A., Fernandez-Hidalgo, O., & al. (2013). Leptomeningeal carcinomatosis: prognostic value of clinical, cerebrospinal fluid, and neuroimaging features. Clin Neurol Neurosurg, 115(1): 19-25.
25. Passarin, M. G., Sava, T., Furlanetto, J., Molino, A., Nortilli, R., Musso, A. M., & al. (2015). Leptomeningeal metastasis from solid tumors: a diagnostic and therapeutic challenge. Neurol Sci, 36(1): 117-123.
26. Enting, R. H. (2005). Leptomeningeal neoplasia: epidemiology, clinical presentation, CSF analysis and diagnostic imaging. Cancer Treat Res, 125: 17-30.
27. Jearanaisilp, S., Sangruji, T., Danchaivijitr, C., & Danchaivijitr, N. (2014). Neoplastic meningitis: a retrospective review of clinical presentations, radiological and cerebrospinal fluid findings. J Med Assoc Thail, 97(8): 870-877.
28. de Azevedo, C. R. A. S., Cruz, M. R. S., Chinen, L. T. D., Peres, S. V., Peterlevitz, M. A., de Azevedo Pereira A. E., & al. (2011). Meningeal carcinomatosis in breast cancer: prognostic factors and outcome. J Neuroonco, 104(2): 565-572.
29. Glantz, M. J., Cole, B. F., Glantz, L. K., Cobb, J., Mills, P., Lekos, A., & al. (1998). Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer, 82(4):733-739.
30. Toyoshima, M., Tsuji, K., Shigeta, S., Tokunaga, H., Ito, K., Watanabe, Y., & al. (2017). Leptomeningeal metastasis from gynecologic cancers diagnosed by brain MRI. Clin Imaging, 41: 42-47.
31. Leal T., Chang J. E., Mehta M., & Robins H. I. (2011). Leptomeningeal Metastasis: Challenges in Diagnosis and Treatment. Curr Cancer Ther Rev, 7(4):319-327.
32. Lombardi, G., Zustovich, F., Farina, P., Della Puppa, A., Manara, R., Cecchin, D., Brunello, A., Cappetta, A., & Zagonel, V. (2011). Neoplastic meningitis from solid tumors: new diagnostic and therapeutic approaches. The oncologist, 16(8), 1175-1188.
33. Brower, J. V., Saha, S., Rosenberg, S. A., Hullett, C. R., & Robins, H. I. (2016). Management of leptomeningeal metastases: prognostic factors and associated outcomes. Journal of Clinical Neuroscience, 27, 130-137.