ITALIAN JOURNAL OF PSYCHIATRY
2024;10:90-93; doi: 10.36180/2421-4469-2024-583

A case of treatment-refractory depression, a leptomeningeal carcinomatosis: a case report

Elisa Salsano[1], Oriana Rossi[2], Cecilia Rispoli[3], Marta Zuccarino[3], Giovanni Carifi[1], Emanuela Landi[1], Loredana Tibullo[4], Nicola Vargas[1]

[1] Geriatric and Intensive Geriatric Care Unit, San Giuseppe Moscati Hospital, Avellino, Italy; [2] Medical department, University of Bari Aldo Moro, Italy; [3] Department of Translational Medical Sciences, University of Naples Federico II, Italy; [4] Medical department, San Sebastiano, Caserta, Italy

Summary

Introduction. Leptomeningeal carcinomatosis is a cancer involving the pia mater and arachnoid mater. Studies have shown that solid tumors, including brain tumors and hematological cancers, could metastasized to leptomeninges. Leptomeningeal carcinomatosis heralds a poor prognosis with limited treatment options.

Case Description. Here we present a 65-year-old male with a history of B-cell lymphoma in regular follow-up, in remission since 2022, who presented an unexpected depressive syndrome in January 2024. This patient had done two ambulatory psychiatric controls that showed a refractory responsive depression of late onset. But before January 2024; he had never manifested any mild psychiatric disorders. In May 2024 during geriatric hospitalization, after performing a geriatric evaluation that showed a high score in geriatric depression scale (GDS) and a defect in Mini mental state examination (MMSE), he underwent magnetic resonance imaging (MRI) brain scan.

Result. The patient had MRI brain scan with contrast completed during his medical admission with lumbar puncture performed by the Neurology team: Pathology resulted and confirmed high-grade malignant neoplasm consistent with large B-cell lymphoma. Then, the patient was seen by Consulation Liason Psychiatry for a chief complaint of depression and anxiety. He had denied any history of depression prior to January.

Conclusion. Leptomeningeal carcinomatosis may rapidly lead to mortality if diagnosis and treatments are not immediately administered. Clinicians should be aware of psychiatric manifestations of neurological disease as early detection especially in elderly patients, and appropriate treatments are the most important prognostic factors for this pathology. As there is a considerable influence on the quality of life for both patients and caregivers, recognition and diagnosis are crucial for appropriate management.

Keywords: refractory depression, carcinomatosis, elderly

INTRODUCTION

Leptomeningeal carcinomatosis (LC), also known as "leptomeningeal metastasis" or "carcinomatosis meningitis," is the involvement by a cancer of the pia and arachnoid mater of the brain with the subarachnoid space in between. It is an uncommon and late complication seen in 5% to 8% of cases of solid tumors and 5% to 15% of cases of hematological cancers. Additionally, it implies a poor prognosis and limited treatment options [1].

About 110,000 new cases of LC are diagnosed each year in the United States. The true incidence of LC is difficult to determine,because, this condition is usually diagnosed during a gross and microscopic examination postmortem at autopsy.

The incidence of LC is increasing due to the improved survival rates secondary to the increased in systemic control of the disease, better imaging, diagnostic modalities,

Correspondence
Elisa Salsano
E-mail: elisa.salsano@gmail.com

How to cite this article:
Salsano E, Rossi O, Rispoli C. A case of treatment-refractory depression, a leptomeningeal carcinomatosis: a case report. Italian Journal of Psychiatry 2024;10:90-93; https://doi.org/10.36180/2421-4469-2024-583

and treatments with therapies that do not cross the blood-brain barrier (BBB). The longer patients live with systemic cancer, the higher the chances of tumor to spread and seeding of the leptomeninges. The median time to identify LC after diagnosis of a solid tumor ranges between 1.2 and 2 years; this time is about 11 months in hematologic cancers [2].

The time from diagnosis to death is about 4 to 6 weeks if left untreated. With treatments, overall survival is approximately 2 to 4 months and markers of poor prognosis are Karnofsky performance score (KPS) less than 60, high CNS disease burden, extensive systemic disease with few treatment options, severe neurologic impairment, and encephalopathy.

CASE REPORT

A 65-year-old patient was admitted to the geriatric department for asthenia, abulia, fecal incontinence of new onset and weight loss of about 7 kg in the past 2 months. In past medical history-he presented type II diabetes mellitus, depression of mood tone arising in the last 6 months and a non-hodking large cell lymphoma of the facial massif treated with RT and CHT in clinical remission since 2022. The home drug therapy was venlafaxine 75 mg die, metformin 500 mg x 3 die, lansoprazole 30 mg die and dapagliflozin 10 mg die.

In January 2024 the patient manifested depressive symptoms for the first time so he went to a pshichiatrician manifesting marked abulia and lack of motivation, so escitalopram 10 mg 1/2 cp for 7 days was prescribed, later to be increased to 1 cp die. At a follow-up visit made after 60 days the patient showed no improvement in symptoms, indeed, the mood deflection appeared to be worsening, so the specialist modified the therapy by discontinuing ciatlopram and starting venlafaxine 75 mg 1/2 cp for 7 days and thereafter 1 cp die.

During hospitalization for the patient's refusal to feed, was placed a PICC to perform parenteral nutrition and was requested a psychiatric evaluation that gave indication to stopped venlafaxine and replace it with escitalopram 20 md die and levosulpiride 24 mg tid.

To investigate weight loss was performed a PET TC and a gastroscopy both negative. Finally, the cranial TC showed a shaded hyperdense area of about 8 mm in the knee of the right corpus callosum, and a minimal asymmetry of the right frontal horn of the lateral ventricle of doubtful interpretation. So, it was recommended to supplement the find with contrast-enhanced encephalic MRI.

The MRI found extensive signal alterations of the periventricular white matter, corpus callosum and deep nuclei with caudal extension to the midbrain through the cerebral peduncles bilaterally (hyperintense in the T2/FLAIR sequences and hypointense in the T1-weighted). These areas showed also slight restrictions of the DWI-weighted signal and foci of pathological impregnations especially of the ventricular ependyma and splenium of the corpus callosum.

The ventricular system so was asymmetric for a major left hemi-section. The radiological overview concluded for images compatible with cerebral lymphomatosis in the first hypothesis which deserved a direct examination.

To complete the diagnosis a lumbar puncture was performed by the Neurology team that showed a pleocytosis, hypoglycorrhachia, and elevated protein in cerebrospinal fluid (CSF) study. At cytological examination of CSF there were amorphous serous materials of few scattered small lymphocytic elements confirmed by cytofluorimetric study as plausible infiltration of B-cell lymphoproliferative disease. There were presented a 16% of B lymphocyte population immunophenotype positive for CD 19, CD 20, CD 22, CD 38, LAMBDA monoclonality and negative for CD 5, CD 10, CD 23, CD 200, CD 103.

During the hospitalization, the patient regularly practiced physiotherapy to reduce immobilization and was treated with palliative cures with corticosteroids, antidepressants and antiepileptics for his ineligibility to chemotherapy for his severe comorbidities and compromised vital functions.

Twenty-five days after the diagnose, the patient died for respiratory failure in bronchopneumonia from methicillin-resistant staphylococcus.

DISCUSSION

Depression in old age is common. Prevalence rates among elderly people seen in primary care range from 6.5 to 9% for major depression and from 10 to 25% for clinically relevant depressive symptoms.

But In elderly, there is much clinical and biologic overlap between depression and other organic brain disorders such as dementia, with evidence that late-onset depression may sometimes be a prodrome for other organic disorders, so, careful clinical evaluation and follow-up of late-onset depressives are suggested [3].

Also given the frequency with which depression in geriatric patients can be a prodrome of cognitive impairment, performing a comprehensive evaluation with brain MRI, geriatric multidimensional assessment, and pscicometric testing is necessary [4].

Leptomeningeal involvement in lymphoma is exceedingly rare, only occurring in 6% to 8% of NHL patients. However, the prevalence of LMD in NHL accounts for 5 to 30% of all LMD metastatic cases, with a median prognosis of 2.6 months of survival [5].

Consequently, LMD metastasis presents a poor prognosis, with an overall survival estimated at less than 6 months in duration [5]. Given that specific lymphoma variants have relatively higher rates of CSF dissemination, CSF cytology remains a crucial diagnostic tool for leptomeningeal lymphoma [7]. Unfortunately, multimodal diagnostics in the form of CSF analysis and focal MRI detect leptomeningeal involvement in 7% to 42% of patients, thereby indicating observable variation in accuracy [5]. Compared to solid tumor cancers, LMD from lymphoma occurs more often in the absence of systemic disease or parenchymal involvement and, at times, during remission.

Diagnosis is often challenging, with nonspecific presenting symptoms ranging from headache and confusion to focal neurologic deficits, such as cranial nerve palsies [6].

The initial diagnostic evaluation includes at least a high-quality MRI of the brain and spine and CSF studies. MRI with gadolinium contrast has a sensitivity of 70% and specificity of 77% to 100%. It may detect leptomeningeal enhancement, hydrocephalus, subependymal nodules/deposits (which may also be seen on cerebral convexities), cisterns, and on the tentorium. Spinal cord involvement may show patchy enhancement of nerve roots and extramedullary nodules.

If safe, then diagnostic evaluation should be furthered by a lumbar puncture (LP). In the case of LC, CSF studies usually show mild pleocytosis, hypoglycorrhachia (usually less than 60 mg/dL), and elevated protein (greater than 45 mg/dL). If the glucose levels are very low, then infectious etiologies must be ruled out. In 50% to 70% of cases, it may show elevated opening pressure (greater than 150 mm) as well. False-negative cytology results are common, and a study shows CSF cytology can have false-negative results of up to 36% when samples are refrigerated for 48 hours. These false-negative results can be minimized by securing a large volume (10 mL) of CSF for cytology, expediting sample processing without additional storage, and obtaining CSF from cisterns or the lumbar region or a site of known leptomeningeal involvement. In most cases, positive CSF studies and suggestive radiographic findings are enough to make a diagnosis, but a negative LP should be followed by at least one additional LP, especially if there is high clinical suspicion. The sensitivity of cytology is 50% to 60% after the first LP and approaches 85% to 90% with the second collection [7].

CSF tumor markers also have been evaluated as an aid in the diagnosis, but the relative lack of sensitivity and specificity limits this modality from routine use. Nonetheless, this method is an option in certain tumors if all other workup is negative. Certain tumor markers that can be tested include CEA in adenocarcinomas, alpha-fetoprotein in hepatocellular and testicular carcinomas, and beta-human chorionic gonadotropin in choriocarcinomas and testicular carcinomas. There is also some data on determining VEGF levels in CSF, but further research is yet to be conducted on the topic.

Recently, cell-free DNA in CSF has undergone evaluation to detect tumor-specific somatic mutations through next-generation sequencing, which may help detect certain tumors.

Rarely, CSF flow studies/ventriculography using Indium 111-DTPA or Technetium-99m labeled albumin may be used to identify CSF flow.

The prognosis of LC remains poor despite advances in therapy. There is a lack of randomized clinical trials, and treatment methods are derived from lower evidence studies or clinical expert opinions. Treatment focuses on improving neurologic deficits, quality of life, and prolonging survival while minimizing toxicity. Commonly, radiation is applied to bulky or symptomatic anatomical lesions followed by IT chemotherapy. CSF flow obstruction is relieved by surgical interventions; however, surgery has a very marginal role in the management of LC. Systemic therapy can be added to the regimen to treat the primary tumor and potentially prolong survival [8].

Palliative and supportive treatment are provided as needed with anti-depressants, anxiolytics, and opioid and non-opioid agents. Psychostimulants should always be provided in addition to pursuing the treatment of the disease/cancer.

IT chemotherapy has shown a survival benefit in retrospective studies. The agent used commonly includes methotrexate (MTX), cytarabine, thiotepa, and sustained release liposomal cytarabine. Studies have shown superior efficacy of sustained-release cytarabine compared to MTX.

Aseptic/chemical meningitis is a common complication that is manageable with steroids. Infectious meningitis (commonly implicated organism is *Staphylococcus epidermidis*), seizure, myelosuppression, and leukoencephalopathy are some other complications encountered.

The use of cytfluorimetry on CSF may allow diagnosis avoiding invasive procedures.

CONCLUSION

In elderly the onset of depression should be carefully investigated to rule out underlying organic pathology. The minimum brain imaging to be performed is a brain MRI and neurocognitive tests because as is known it can be the onset of dementia. But if the patient's history is positive for neoplastic pathology, it is more appropriate to perform contrast-enhanced MRI to rule out a brain localization of the neoplasm. Even in these cases, treating psychiatric symptoms appropriately is still part of palliative care and improves the quality of life of the patients and caregivers.

The late-onset depressives have a different presentation, more frequent relapses, and a greater association with medical disorders, dementia, and aging-related biologic changes than early-onset geriatric depressives. Longitudinal investigations of geriatric depressed patients are needed in order to study the frequency and time of occurrence of various clinical outcomes and identify predictors of outcome in late- and early-onset geriatric depression [9].

Conflict of interest statement

The authors declare no conflict of interest.

Funding

None.

Ethical consideration

None.

Authors' contribution

O.R. case report; E.L. introduction; G.C. abstract; C.R. introduction; N.V. e E.S. discussione; L.T. conclusione; M.Z. references

References

1. Batool A, Kasi A. Leptomeningeal Carcinomatosis. 2023 Mar 27. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan. PMID: 29763037.
2. El Shafie RA, Böhm K, Weber D, et al. Outcome and prognostic factors following palliative craniospinal irradiation for leptomeningeal carcinomatosis. Cancer Manag Res. 2019;11:789-801. https://doi.org/10.2147/CMAR.S182154.
3. Sunderland T, Lasser RA, Levin R, et al. Depression in the elderly: biologic considerations. Int Clin Psychopharmacol. 1997;12 Suppl 7:S15-8. https://doi.org/10.1097/00004850-199712007-00003. PMID: 9476135.
4. Wang SM, Han KD, Kim NY, et al. Late-life depression, subjective cognitive decline, and their additive risk in incidence of dementia: A nationwide longitudinal study. PLoS One. 2021;16(7):e0254639. https://doi.org/10.1371/journal.pone.0254639. PMID: 34260630; PMCID: PMC8279395.
5. Nayar G, Ejikeme T, Chongsathidkiet P, et al. Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget. 2017;8:73312-73328. https://doi.org/10.18632/oncotarget.20272.
6. Taylor JW, Flanagan EP, O'Neill BP, et al. Primary leptomeningeal lymphoma: International Primary CNS Lymphoma Collaborative Group report. Neurology. 2013;81:1690-1696. https://doi.org/10.1212/01.wnl.0000435302.02895.
7. Nolan CP, Abrey LE. Leptomeningeal Metastases from Leukemias and Lymphomas. Cancer Treat Res. 2005;125:53-69. https://doi.org/10.1007/0-387-24199
8. Wang N, Bertalan MS, Brastianos PK. Leptomeningeal metastasis from systemic cancer: Review and update on management. Cancer. 2018;124(1):21-35. https://doi.org/10.1002/cncr.30911. Epub 2017 Nov 22. PMID: 29165794; PMCID: PMC7418844.
9. Alexopoulos GS, Young RC, Meyers BS, et al. Late-onset depression. Psychiatr Clin North Am. 1988;11(1):101-15. PMID: 3288975.