

CASO CLÍNICO/CASE REPORT

Leptomeningeal Carcinomatosis in a Patient with Lung Adenocarcinoma Treated with Whole Brain Radiation Therapy and Intrathecal Chemotherapy

Carcinomatose Leptomeníngea num Doente com Adenocarcinoma do Pulmão Tratada com Radioterapia Holocraniana e Quimioterapia Intratecal

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DOI: <https://doi.org/10.46531/sinapse/CC/200064/2020>**Informações/Informations:**

Caso Clínico, publicado em Sinapse, Volume 21, Número 1, janeiro-março 2021. Versão eletrónica em www.sinapse.pt
Case Report, published in Sinapse, Volume 21, Number 1, January-March 2021. Electronic version in www.sinapse.pt
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Keywords:

Cranial Irradiation;
Lung Neoplasms;
Meningeal Carcinomatosis;
Antineoplastic Agents/
therapeutic use.

Palavras-chave:

Antineoplásicos/uso
terapêutico;
Carcinomatose Meníngea;
Irradiação Craniana;
Neoplasias do Pulmão.

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Recebido / Received: 2020-11-18

Aceite / Accepted: 2020-12-25

Publicado / Published: 2021-04-16

Abstract

Leptomeningeal carcinomatosis is a rare complication of several types of cancer. There are many possible clinical features, and the diagnosis is made with brain imaging and cytological analysis of cerebrospinal fluid. Treatment is widely debated and, concerning overall survival, there does not seem to exist a treatment option which is definitely superior. The present work describes the case of a 53-year-old man diagnosed with leptomeningeal carcinomatosis secondary to lung adenocarcinoma, who was treated with whole brain radiation therapy and, upon relapse, with intrathecal chemotherapy, showing both an above-average overall survival and a high performance status.

Resumo

A carcinomatose leptomeníngea é uma complicação rara de alguns tipos de neoplasia. As manifestações clínicas possíveis são várias, sendo o diagnóstico feito por meios imagiológicos e análise citológica do líquido cefalorraquidiano. O tratamento é um motivo de debate, pois não parece existir uma opção de tratamento que seja claramente superior, no que toca à sobrevida. Este estudo de caso descreve o caso de um homem de 53 anos diagnosticado com carcinomatose leptomeníngea secundária a adenocarcinoma do pulmão, que foi tratado com radioterapia holocraniana e, aquando da recidiva, quimioterapia intratecal, revelando tanto uma sobrevida como um estado funcional acima da média.

Introduction

The central nervous system is a possible site where distant spread occurs for certain types of cancer. Leptomeningeal metastasis are a rare complication, albeit with a rising incidence and a bad prognosis.¹ The increasing incidence can be explained by a number of factors, such as improvement in systemic control of the primary cancer, which leads to improved survival, improvements in imaging and diagnostic accuracy and also the use of chemotherapeutic agents that do not cross the blood-brain barrier.² The most frequently associated solid cancers are, in descending order of frequency, breast adenocarcinoma, lung adenocarcinoma and malignant melanoma. However, leukemia and lymphoma are the most frequent causes of leptomeningeal metastasis.¹

The clinical manifestations of meningeal involvement are varied, and they are caused by an increase in intracranial pressure (ICP), infiltration or compression of the brain parenchyma, disruption of the blood-brain barrier, among others.³ Of note, one of the signs of increased ICP is the presence of plateau wave phenomena, which are acute elevations of ICP which translate clinically into paroxysmal neurological symptoms triggered by postural changes.⁴ Other characteristic symptoms and signs of meningeal involvement include headache, gait disorders (apraxia or ataxia), cognitive impairment, loss of consciousness (usually due to seizures), cranial nerve dysfunction or spinal nerve root compromise.³

Before magnetic resonance imaging (MRI), the gold standard for the diagnosis of leptomeningeal carcinomatosis was cerebrospinal fluid (CSF) cytology.⁵ Although it is still important and required for a confirmed diagnosis, MRI has become fundamental.⁶ Moreover, the combination of clinical features and suggestive imaging features is sufficient for a probable diagnosis, even with a negative CSF cytology.⁷ However, the use of MRI has no prognostic impact, and a positive CSF cytology is sufficient for diagnosis even with a normal MRI.^{5,6} In rare cases, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can be useful for the diagnosis.⁸

Leptomeningeal metastasis can be classified into two types: type 1, in case the diagnosis is confirmed by positive CSF cytology or biopsy; type 2, in case the diagnosis is made using only clinical and imaging features.⁶

There is a wide therapeutic arsenal for the treatment of this condition, including optimization of the treatment of the primary cancer, whole brain radiation ther-

apy (WBRT) or focal radiation therapy and intrathecal chemotherapy (ITC).⁹ The efficacy of these treatments is controversial, and there exists data which supports the preferential use of several of these options.^{9,10} However, the role of WBRT is becoming less important.¹¹ EANO-ESMO guidelines recommend patient stratification and therapeutic decision according to prognosis, the type of meningeal metastasis, the presence of active cerebral metastasis and the status of the primary cancer; however, the level of evidence for therapeutic recommendations is low and the therapeutic decision must always be individually tailored.^{6,11}

Life expectancy after the diagnosis of leptomeningeal metastasis depends on the primary cancer. The median overall survival of non-small cell lung cancer leptomeningeal metastasis is 3 to 8.7 months.⁹

This report describes a case of leptomeningeal carcinomatosis secondary to lung adenocarcinoma, treated successfully with WBRT and, upon relapse, ITC.

Case Report

In September 2019, a 53-year-old male went to the ED of Instituto Português de Oncologia de Lisboa Francisco Gentil complaining of severe holocranial headache, which woke the patient up from sleep, loss of visual acuity, scintillating scotomata and loss of balance, with a 1-week evolution period. There were no significant findings on neurological examination. He underwent a head computerized tomography (CT) scan, which showed nonacute ischemic lesions in the posterior fossa, which would not explain the clinical picture. However, the previous records of the patient showed a CT scan from 2010, which did not show these findings. There was also a slight supratentorial ventriculomegaly in relation to this previous exam.

The patient had a history of adenocarcinoma of the lower lobe of the right lung, which was diagnosed in December 2010 by transthoracic biopsy (cT3N0M0), and he underwent lobectomy in January 2011, leading to the definitive diagnosis of mixed adenocarcinoma (invasive adenocarcinoma with areas of bronchioloalveolar adenocarcinoma), pT3N2M0. Genetic analysis revealed an insertion in exon 20 of the *EGFR* gene (a mutation which confers resistance to tyrosine kinase inhibitors) and wild-type *ALK* and *PDL1* genes. Adjuvant chemoradiotherapy was given, with carboplatin and paclitaxel until May 2011, and at this point a state of complete

remission had been achieved.

In December 2016, in a follow-up appointment, the patient complained of sciatic pain and paresthesia along the right lower member, and a bony metastasis was suspected in L5, which was confirmed in January 2017 by biopsy of the lesion shown in a CT scan. The biopsy showed a histological and genetic profile compatible with a metastasis of lung adenocarcinoma. The patient underwent single-dose external radiation therapy in March 2017, with complete response, which was documented in a positron emission tomography (PET) scan at two times: March 2017 and January 2018.

In July 2018, an increase in the number of pulmonary nodules in the left superior lobe was documented, as well as the appearance of *de novo* bilateral micronodules, which raised suspicion for progression of the neoplastic process. This motivated hospital admission for treatment with cisplatin and pemetrexed, with radiologically documented improvement.

In May 2019, a lumbar spine CT scan revealed a progression of the metastatic lesion of L5, with a pathologic fracture and compromise of the root of the right S1 nerve. Therefore, the patient underwent a second round of single-dose 20 Gy external radiation therapy, with clinical improvement.

Following the described episode from September 2019, we admitted the patient to the ward, and he underwent a head MRI, which showed aspects suggestive of leptomeningeal dissemination of the primary cancer, namely an effacement of the cerebral gyri in the left frontoparietal convexity, with FLAIR hyperintensity in the sulci (**Fig. 1**). Lumbar punctures were performed and 10 mL of CSF were collected, and on the second attempt, neoplastic cells positive for TTF-1 were found on cytological analysis (**Fig. 2**). Given the genetic profile, which excluded the patient from receiving targeted therapy, he underwent WBRT (30 Gy) and was treated with dexamethasone, and the follow-up MRI in February 2020 did not reveal aspects of meningeal disease.

In follow-up appointments, the patient complained of worsening of symptoms in May 2020, with sudden onset lipothymia upon standing up and visual disturbances in the right hemifields, which raised suspicion for plateau wave phenomena. On fundoscopy, there was slight bilateral papilledema. Given the apparent progression of the meningeal disease, the patient was started on acetazolamide and underwent head and neuroaxis

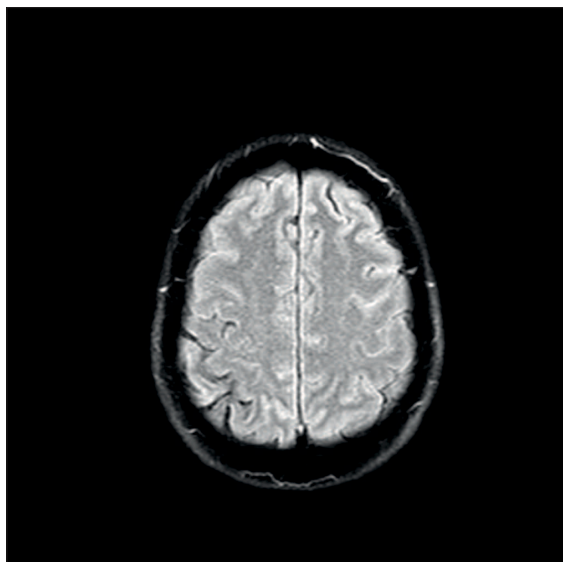


Figure 1. FLAIR imaging showing slight hyperintensity of the left hemisphere frontal sulci.

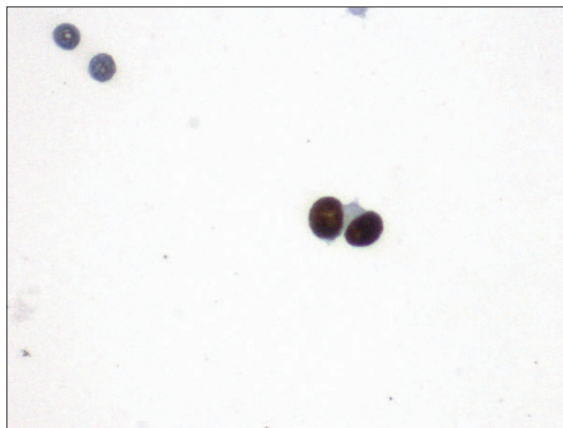


Figure 2. CSF immunohistochemistry with TTF1-positive cells.

MRI, to document the progression of the disease, and a cisternography with 99m Tc-DTPA to identify possible blockages in CSF circulation and verify eligibility for intrathecal chemotherapy. The MRI showed once again signs of leptomeningeal involvement, with some gadolinium-enhancing areas and FLAIR hyperintensities, as well as a slight ventriculomegaly. The cisternography showed normal CSF circulation. The lumbar puncture previous to this exam showed an opening pressure of 15.5 cmH₂O, a protein concentration of 67 mg/dL and no neoplastic cells on cytology. The neurological exam upon admission showed slight impairment of episodic memory, partial bilateral loss of visual acuity, bilateral papilledema and hemorrhages around the optic disc, more intense in the right eye. The patient also had a

mild ataxic gait. We treated the patient with 30 mg of intrathecal cytarabine, twice per week for one month. After treatment, there was clinical improvement, with lowering of headache intensity and frequency of plateau wave phenomena. The patient was discharged and a treatment plan of continuation of intrathecal chemotherapy was devised. In September 2020, the patient had a survival time of 12 months since the diagnosis of leptomeningeal carcinomatosis and a Karnofsky performance scale of 80.

Discussion

Leptomeningeal carcinomatosis is still a disease with a bad prognosis. Although rare, the incidence is growing. Normally it has a very aggressive clinical course but some patients have a more insidious progression, such as our patient. A high level of suspicion is needed in symptomatic cancer patients, and as our case clearly shows there is opportunity for meaningful therapeutic interventions. As such, the recognition of this clinical entity is fundamental. The studies that were conducted regarding treatment are not consensual in which is the best therapeutic option for every situation, and more research is necessary in this area. ■

Acknowledgement

We would like to thank Dr. Saudade André for providing us with images of the cerebrospinal fluid cytology and immunohistochemistry.

Agradecimento

Gostaríamos de agradecer a colaboração da Dra. Saudade André no fornecimento das imagens da citologia e respetiva imunohistoquímica do líquido cefalorraquidiano.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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