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REVIEW ARTICLE

Neoplastic meningitis. Review of a clinical series☆

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Abstract
Introduction: The increase in the ageing population in the last decades has led to an increased frequency of cancer-associated complications. Among these, neurological disorders stand out, as they appear in 10-30% of patients with systemic neoplasia. Neoplastic meningitis accounts for 4-15%of patients with solid tumours and it has a poor prognosis. The objective of this paper is to describe the clinical, imaging and prognostic characteristics as well as cerebrospinal fluid findings in a series of neoplastic meningitis.
Background and development: We performed a retrospective review of all patients admitted to the Hospital Universitario of Gran Canaria Dr. Negrín with clinical suspicion of neoplastic meningitis between 1990 and 2008.

We selected 37 patients with an average age ranging from 15 to 75 years old. A total of 81.8% of the cases in which a primary tumour was found were associated with solid tumours (24.2%were located in the breast, and 24.2%in the lung). The most frequent sign of cranial nerve dysfunction was dyplopia, which was observed in 32.4%of the cases. The average survival rate after diagnosis was 87.9 days (12.6 weeks). The cerebrospinal fluid cytology was positive in 46.4% of the cases.
Conclusion: Neoplastic meningitis is a severe complication of both solid and haematological tumours. We stress the importance of maintaining a high level of suspicion to achieve early diagnosis, since the average survival probability for neoplastic meningitis patients is low.

PALABRAS CLAVE
Meningitis carcinomatosa;
Meningitis neoplásica;

Meningitis neoplásica. Revisión de una serie hospitalaria

Resumen
Introducción: El progresivo envejecimiento de la población en las últimas décadas ha provocado un aumento en la frecuencia de aparición de las muchas complicaciones que

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Líquido cefalorraquídeo;
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Resonancia magnética

se asocian al cáncer. Entre ellas destacan las neurológicas, que aparecen en un 10-30% de los pacientes con neoplasias sistémicas. La meningitis neoplásica aparece en un 4-15% de los pacientes con tumores sólidos y se asocia a un mal pronóstico. El objetivo de este trabajo es describir las características clínicas, licuorales, de imagen y pronósticas en una serie de meningitis neoplásica.

Fuentes y desarrollo: Se realizó una revisión retrospectiva de todos los pacientes ingresados en el Hospital Universitario de Gran Canaria Dr. Negrín con sospecha de meningitis neoplásica entre los años 1990 y 2008. Se seleccionaron 37 pacientes, con un rango de edad entre los 15 y los 75 años. De los 33 casos en los que se identificó un tumor primario, 27 (81,8%) estaban asociados a tumores sólidos (24,2% de mama y 24,2% de pulmón). La diplopia fue la manifestación de disfunción de nervios craneales más frecuente, observándose en 12 casos (32,4%). La supervivencia media tras el diagnóstico fue de 87,9 días (12,6 semanas). La citología del líquido cefalorraquídeo fue positiva en 12/26 casos (46,4%).

Conclusión: La meningitis neoplásica es una complicación grave de los tumores tanto sólidos como hematológicos. Es necesario mantener un alto nivel de sospecha que permita establecer un diagnóstico precoz, puesto que la supervivencia media en los pacientes con meningitis neoplásica es baja

Introduction

Progressive ageing of the population over the last few decades has caused a significant increase in the incidence of different types of cancer in our society.[1-3] At the same time, their treatment has improved, prolonging survival after diagnosis.[4] This has increased the appearance of many complications associated to this disease. Neurological complications among cancer patients stand out, as they appear in 10%30% of cases.[5,6]

Neoplastic meningitis (NM) is the infiltration of the meninges by tumour cells, which are spread through the cerebrospinal fluid (CSF).[7,8] It was first described by Eberth in 1870.[9] A relatively common complication in systemic cancers, it appears in 3%15% of patients with solid tumours (carcinomatous meningitis) and in 5%15% of patients with haematological tumours (lymphomatous meningitis and leukemic meningitis).[10-17]

This paper is to describes the clinical, imaging and prognostic characteristics as well as cerebrospinal fluid findings in a series of NM cases.

Material and methods

We performed a retrospective review of all patients admitted to the Hospital Universitario de Gran Canaria Dr. Negrín with clinical suspicion of NM between 1990 and 2008. This is a tertiary hospital that covers a health area of approximately 450,000 inhabitants.

All patients admitted to the Neurology Department were given a discharge report, which is stored on a computerised database (FILEMAKER PRO version 5.5®). All admittances during the study period were selected and reviewed, including all patients admitted with suspected NM, according to the criteria set out by the authors of this paper (please see further on). Patients admitted to other departments were found using the hospital Coding Department. A search was performed using the terms "neoplastic meningitis," "carcinomatous meningitis", "meningeal carcinomatosis", "leptomeningeal carcinomatosis", "lymphomatous meningitis" and "leukemic meningitis".

All patients initially selected were reviewed by two of the authors. In all cases selected, we reviewed epidemiological data (age and gender), clinical data (whether there was fever or not, headache, neck stiffness, nausea or vomiting, cranial nerve abnormalities, consciousness impairment or other clinical focus and/or seizures), oncological data (whether there was a known primary tumour and its location), laboratory values (basic blood tests, biochemistry and erythrocyte sedimentation rate), CSF parameters (cytobiochemistry, microbiological analysis and cytology) and neuroimaging technique results (computerised tomography [CT scan] and brain magnetic resonance imaging [MRI] for every case). We specifically looked for diagnosis through culture, serology or polymerase chain reaction, in both blood and CSF, of aerobic and anaerobic bacteria, *mycobacteria, Treponema pallidum* and neurotropic virus (human immunodeficiency, Epstein-Barr, cytomegalovirus, herpes simplex and varicella-zoster viruses). In cases where fungi detection techniques had been carried out, these results were also collected. Disease evolution was reviewed in all cases.

Carcinomatous meningitis diagnosis was based on clinical data, cerebrospinal fluid and neuroimaging data. Neoplastic meningitis was diagnosed as the following: 1) presence of neoplastic cells in the CSF; 2) CSF cellularity >10 leukocyte count, with negative microbiological studies and findings in the brain MRI or CT scan compatible with neoplastic meningitis; 3) CSF cellularity>10 leukocyte count, with decreased CSF glucose (<50% plasma glucose) and/or high protein (protein in the CSF> 45mg/dl), as long as the aforementioned microbiological studies were negative and there was a previous history of malignant neoplasm or diagnosis of it during admittance or follow-up.

Diagnostic findings in brain MRI or CT scans considered compatible with a NM included: 1) diffuse leptomeningeal enhancement; 2) meningeal thickening; 3) multiple nodular deposits in the subarachnoid space, cerebellar or cortical surface; and 4) tumour masses, with or without hydrocephalus.

Results

Thirty-seven patients were chosen, 20 males (54.1%) and 17 females (45.9%), aged between 15 and 75 years old. The mean age was 50.5 years old (44.8 years old for males and 56.9 years old for females).

The primary tumour was known about before NM diagnosis in 26 cases (70.3%). In 7 cases, the primary tumour was diagnosed after the NM diagnosis, 5 of them after CSF analysis, 1 after a cortical biopsy and another after necropsy. In 4 cases (10.8%), the primary tumour was not diagnosed. Of these 4 cases, 1 presented positive cytology and 1 had hepatic lesions compatible with unknown primary metastases.

Among the 33 cases with a known primary tumour, 27 (81.8%) were solid tumours. Of these, 8 (24.2%) corresponded to breast cancer; 8 (24.2%) to lung cancer; 5 (15.2%) to primary brain tumours (including a gliosarcoma, a high-grade astrocytoma, an embryonic neuroepithelial tumour, a pineal gland tumour and another of undefined lineage); 3 (9.1%) were prostate adenocarcinoma; 2 cases (6.1%) were ovarian cancer; and 1 (3%) was melanoma. The 6 remaining cases (18.9%) corresponded to types of haematological tumours: 4 were non-Hodgkin lymphoma (12.1%), 1 (3%) was a pre-B acute lymphoblastic leukaemia and 1, (3%) a primary meningeal lymphoma. The frequency of the different tumours is shown in figure 1.

The characteristics for CSF were analysed in 31 of the cases. Their results can be seen in table 1. In 29 cases (93.5%), we saw an alteration in at least 1 CSF parameter (high protein > 45mg/dl, pleocytosis> 10 cell/mm^3, or glycorrhachia < 60-80mg/dl or < 60% of the plasma glucose). In the 2 remaining cases (6.5%), all the CSF cytobiochemical parameters were normal, with a NM diagnosis through positive cytology for malignancy being reached in one of them, and NM diagnosis by compatible image in the other case. There were cytological results in 28 cases. The CSF cytology proved positive for malignant cells in 9 cases (32.1%) with the first lumbar puncture, in 3 (10.7%) on the second and 1 (3.5%) on the third or successive ones. In all, there was positive CSF cytology in 13 cases (46.4%).

In the 6 patients where the CSF was not analysed, NM was diagnosed due to a typical clinical presentation and alterations in the MRI/ CT scan compatible with NM.

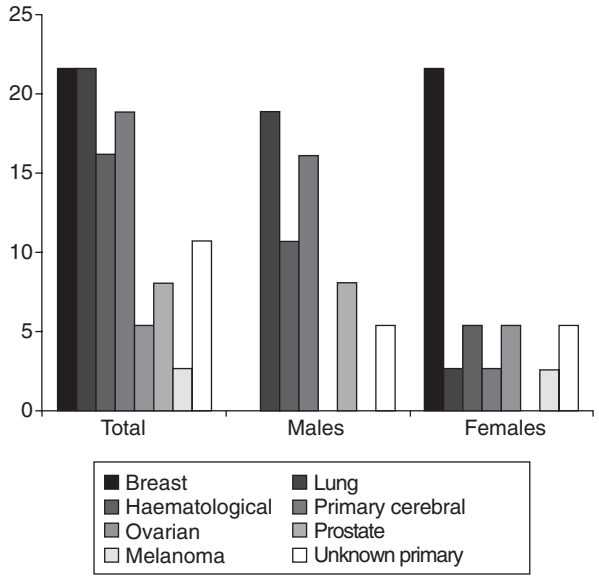

Figure 1 Relative appearance frequency (percentage) of the different primary tumours.

A cranial CT scan was carried out on 30 cases (81%) with findings compatible with NM in 7 of them (23%), and non-suggestive NM alterations in 5 (16.7%). There were no alterations in 18 cases (60%). An MRI of the neuraxis was performed on 28 cases (75.7%). Of these, 21 (75%) showed alterations compatible with NM, 3 (10.7%) showed alterations of another type and 4 (14.3%) were within the normal range. With regards to the alterations found in the MRI, 13 cases (46.4%) presented diffuse leptomeningeal infiltration, 4 cases (14.3%) focal enhancement, 2 cases (7.1%) showed tumoral masses and 3 cases (10.7%) showed subarachnoid and interventricular nodular deposits, with associated hydrocephalus in 2 of them.

The neurological presentation signs and symptoms are summarised in table 2. In 18 cases (48.7%), the clinical presentation was located at just 1 neuraxial level (spinal, posterior fossa or supratentorial) and included the 3 areas in 4 cases (10.8%). Headache was a presentation symptom in 19 patients, with variable characteristics and locations. There were 4 cases with fever (10.8%). Mental status alterations included from changes in level of consciousness (from drowsiness to coma) to its contents (delirium, cognitive impairment). These types of alterations were seen in 7 of the cases analysed (18.9%).

Table 1 Cerebrospinal fluid parameters at the time neoplastic meningitis is diagnosed

	Positive/ totals (%)	Mean	Range
Proteins (mg/ dl)	27/ 31 (87.1)	277.78	4-2,002
Glucose (mg/ dl)	20/ 31 (64.5)	62.02	3-478
Cellularity (cell/ mm^3)	21/ 31 (67.7)	40.17	1-1,750

Table 2 Signs and symptoms of presentation for neoplastic meningitis

	No. of cases (percentage)
Symptoms	
Headache	19 (51.4)
Nausea, vomiting	3 (8.1)
Weakness	13 (35.1)
Sensory disturbance	11 (29.7)
Altered mental state	7 (18.9)
Diplopia	12 (32.4)
Altered coordination	4 (10.8)
Radicular or spinal pain	3 (8.1)
Seizures	2 (5.4)
Signs	
Altered mental state	7 (18.9)
Meningism	2 (5.4)
Cranial nerve	
II	5 (13.5)
III	4 (10.8)
IV	1 (2.7)
V	6 (16.2)
VI	7 (18.9)
VII	1 (2.7)
VIII	0
IX	2 (5.4)
X	3 (8.1)
XI	0
XII	1 (2.7)
Cerebellar signs	5 (13.5)
Motor disorder	10 (27.0)
Sensory level	3 (8.1)

II includes both the decrease in visual acuity as well as the presence of papilloedema.
Motor disorder includes hemiparesis, paraparesis or tetraparesis.
Sensory disorder includes facial sensory symptoms.

Focal neurological involvement data was seen in 22 cases (59.5%). Of these, 16 had cranial nerve involvement (43.2%), both independently (3 cases) and associated to other focal signs.

We obtained reliable data in 25 of the 37 cases studied for evolution. All of them died between the NM diagnosis date (3 cases; 12%) and 12 months later. Seven cases (28%) died in the first month after NM was diagnosed, two of them within the first week of evolution. The remaining cases were equally distributed among the following 2 trimesters and the second semester from the diagnosis (3 cases, 12% per period). The moment of death could not be defined in 6 cases. In the 4 cases where a primary tumour was not found, the patient died in the first month after diagnosis. The patient who presented CSF without any cytobiochemical or cytological anomalies died 6 months after diagnosis. The mean survival rate after diagnosis was 87.9 days (12.6 weeks).

Discussion

Neoplastic meningitis appears in 3%-15% of all cancer patients.[10-17] This percentage increases to up to 19% in some autopsy series.[18] Generally, it is seen in advanced states of neoplastic disease, although it is not exclusive to these phases.[12,19-21] Its appearance leads to a significant increase not only in morbidity but in mortality.

Primary tumours more frequently associated to cases diagnosed with NM are breast, lung and melanoma carcinomas with a relative frequency of 27%-50%, 22%-36% and 12% respectively.[12,13,17] In our series, we obtained similar data in the first two tumours (21.6% in each case). However, we found only 3% of cases associated to melanoma, which could be related to the low incidence rate of melanoma in our community, one of the lowest in Europe.[22] In our study, the third most common tumour consisted of by a group of haematological neoplasms, making up 16.2% of the cases included. A primary concomitant brain tumour was seen in 13.5% of patients, a result similar to other studies (10%-32%).[23] In published series, unknown primary carcinomas constitute 1%-7% of all NM cases.[12] In our series, this percentage increased to up to 10.8%, making it the fifth most common. This difference is perhaps due to insufficient research of these cases given the short mean survival of the patients after NM diagnosis. Consequently, a high level of clinical suspicion must be maintained to diagnose NM, given that while a previous cancer history supports NM diagnosis, in 29.8% of cases in our series the primary tumour was not discovered before the neurological symptoms.

The appearance of multi-focal neurological symptoms is characteristic of NM.[11-15,17,20,24-28] The most frequent symptom in our series was headache (51.4%). The analysis of cases with headache did not make it possible for us to find characteristics that can be assumed to be typical of NM; however, our study design (based on retrospective case review) was not appropriate for this purpose. Alterations in mental state and seizures were observed in 18.9% and 5.4% of our cases respectively, a lesser frequency than those described in literature. In the case of mental state alterations, these differences could be related to the type of study, as some of the patients were not assessed by a neurologist on admission and data collection was retrospective, so subtle mental state alterations might have been missed. In the case of seizures, we did not find any factor to justify why they appeared less frequently in our series. Cranial nerve involvement is common in NM cases; that the involvement of both the optical nerve and the facial nerve was less frequent in our series is notable, although we think these variations should be understood because it was a study where data collection was carried out retrospectively, with a more than likely loss of subtle focal data. In 48.7% of our cases, we saw involvement data at just one level. This percentage is similar to that found in other studies, in which up to 53% is seen.[20] Because of this, it is important to maintain NM suspicion when there are subacute or chronic neurological symptoms, even when these are limited to just one neuraxial level.

Neoplastic meningitis diagnosis has increased over the last few years, probably due to the lengthy survival of patients with metastases and the improvements in diagnostic

procedures. The most important diagnostic test is the CSF test, generally obtained via a lumbar puncture.[11-13,15,18,24-26,29] In our series, only 2.7% were normal in the four CSF parameters collected (cellularity, high protein, glycorrhachia and cytology). The most commonly-detected alterations were high protein concentration (87.1%) and pleocytosis (67.7%). These results coincide with those described in previous studies with percentages between 79%-91% and 72%-79%, respectively.[12,14,17,20,24,25] Positive CSF cytology for malignant cells is the standard diagnostic method for NM. However, its sensitivity is not very high, with positive percentages of between 45% for the first analysis and 80% for the second determination.[12,18] We recommend that the CSF volume extracted should be around 8-10 cc, as this increases the sensitivity of the test with respect to smaller CSF analysis volumes.[12,14] In our series, the return for cytological studies was low, with a positive percentage of 46.4% despite repeated CSF extractions, which could be related to analyses with scarce CSF volumes. It is generally considered that carrying out more than two lumbar punctures does not significantly increase its sensitivity,[12] as long as the CSF volume extracted is the correct amount.

Magnetic resonance imaging with gadolinium can establish or confirm the diagnosis of some patients with typical clinical presentation with negative cytology.[26,30,31] In our work, cranial CT scan showed findings compatible with NM diagnosis in 23% of cases where it was carried out. This percentage was increased to up to 75% when a neuraxial MRI was carried out. This complementary test was considerably important for NM diagnosis in 64.8% of cases with negative cytology, and even more so in the 2.7% that did not show any alterations in the CSF parameters.

We did not take the time to analyse other NM diagnostic methods, such as CSF bio-chemical markers,[30] as their use is still not established as a regular test at our hospital.

The average survival rate for patients with non-treated NM is 4 to 6 weeks, reaching up to 4-6 months in some cases where the proper treatment is given.[12,32-36] In our series, the mean survival rate was 87.9 days (12.6 weeks), according to the results obtained in 25 of the cases for which we could track the evolution. No exact data was available for the rest of the cases, whether due to a lack of thoroughness when collecting information on the clinical histories or due to lack of information when some patients were transferred from other centres. We must take into account that our hospital is the reference point for half of the population of Las Palmas province, which includes not only the northern area of the island of Gran Canaria but also Lanzarote. Once the initial diagnosis was established, these patients were once again transferred to their corresponding centres, which meant there was a loss of data regarding their later follow-up.

We recognise the limitations of research such as this, in which both patient selection and also data collection were carried out retrospectively. It is probable that NM incidence was understated, as there might have been patients who were admitted to hospital in a terminal phase of their base disease and who were not thoroughly checked to see if there were any associated complications. On the other hand, we did not take patients assessed only by the Neurology Department, which means that there were possibly cases admitted with complications to their base disease and on which an aetiological diagnosis had not been carried out. Given that data collection was also retrospective, subtle data regarding neurological focal involvement might have been lost. In addition, not all the cases had a CSF study, so it was not possible to establish definitive positive values for that parameters. Although the results obtained do not provide any substantial developments to aspects of NM already known, we believe a study of these characteristics does indeed corroborate some general ideas regarding their behaviour. We recommend that a well-designed prospective study should be carried out to help to establish the possible prognostic factors that would facilitate selecting patients who could benefit from specific treatments.

To summarise, NM diagnosis requires a high level of clinical suspicion, because although it generally appears in advanced neoplastic disease, it could be a symptom of an unknown tumour. It should be suspected in subacute and chronic neurological symptoms with multi-focal involvement, without forgetting cases where the symptoms are more localised. Equally, although the cytology for malignant CSF cells is the only sure diagnostic method, the combination of typical symptoms and compatible neuroimaging studies are suitable on their own to establish NM diagnosis.

The importance of early diagnosis in these patients has always been accepted, as administration of proper treatment can improve or stabilise their symptoms, and be beneficial for survival; this is true not only in cases of known metastases, but also in those with no history of neoplasms. In our series we did not obtain sufficient data to establish the benefits of early diagnosis, as our study design was not appropriate for this purpose. However, citing a statement common among clinicians, "the absence of evidence does not mean evidence of absence", which is why we believe that future efforts should be geared towards improving early diagnosis and treatment of a pathology that currently has a sombre prognosis.

Conflict of interest

The authors declare no conflict of interest.

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