Chronic and Subacute Meningitis: Differentiating Neoplastic From Non-Neoplastic Etiologies

The Neurohospitalist
2018, Vol. 8(4) 177-182
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DOI: 10.1177/1941874418773924
journals.sagepub.com/home/NHO

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Abstract

Background and Purpose: Although incidence rates vary, infectious, autoimmune, and neoplastic diseases can all cause chronic and subacute meningitis (CSM). We report a Latin-American, single center, CSM case series, analyzing the main clinical characteristics as well as ancillary diagnostic methods differentiating neoplastic from non-neoplastic etiologies. **Methods:** Retrospective review of CSM cases from a single center in Buenos Aires, Argentina. **Results:** Seventy patients with CSM diagnosis were identified, 49 with neoplastic and 21 with non-neoplastic meningitis. A history of previous cancer was significantly higher in neoplastic cases, whereas prevalence of autoimmune disease and fever was more common in non-neoplastic meningitis. C-reactive protein values were higher in non-neoplastic CSM, as was pleocytosis in cerebrospinal fluid analysis. The most frequent etiologies were breast and lung cancer for neoplastic meningitis cases; and idiopathic, tuberculous, and fungal infection for non-neoplastic cases. **Conclusions:** Chronic and subacute meningitis diagnosis is challenging in daily neurological practice. The results we report contribute information from Latin America regarding etiologies of CSM, which can be identified after a comprehensive evaluation in a majority of cases.

Keywords

chronic meningitis, subacute meningitis, leptomeningitis, pachymeningitis, neoplastic meningitis

Background and Purpose

Distinct from acute meningitis, chronic and subacute meningitis (CSM) is defined as inflammation of brain and spinal cord meninges evolving over weeks or months.¹⁻³ Infectious, autoimmune, and neoplastic causes have been identified, with incidence varying between countries and regions. Infectious etiologies, particularly meningeal tuberculosis (TB), are more frequent in under-developed countries.^{4,5} Regional differences in socioeconomic level, immunization status,^{6,7} migration patterns, travel history, as well as local impact of disorders such as lupus erythematosus,⁸ sarcoidosis,⁹ and Behcet disease^{10,11} could influence prevalence variation.^{12,13}

Clinical history and diagnostic methods including magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and serum tests are essential to establish the cause and promptly identify treatable cases. Therapeutic strategies vary depending on whether infectious, inflammatory, or neoplastic causes are suspected.¹⁴

Herein, we report a single center CSM case series from Latin-America. Our aim was to analyze clinical characteristics of CSM and determine diagnostic methods to help distinguish neoplastic meningitis (NM) from non-neoplastic meningitis (NNM).

Methods

We conducted a systematic search in our electronic medical record system database using the text terms “chronic meningitis,” “subacute meningitis,” or “meningeal enhancement” at a single center in Buenos Aires, Argentina, between January 2007 and February 2017 (2 cases have been previously published elsewhere).^{15,16} Patients with meningeal

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Table 1. Demographic Findings.

	NM (n = 49)	NNM (n = 21)	All Patients (n = 70)	P Value ^a
Sex, n F (%)	32 (65)	12 (57)	44 (63)	.5
Age, years, median (range)	56 (18-80)	58 (32-81)	56.5 (18-81)	.5
Death (%)	20/28 (71)	3/20 (15)	23/48 (48)	<.0001
Time to diagnosis (median in months, range)	1.5 (1-32)	3 (1-72)	2 (1-72)	.19
Tobacco (%)	24/49 (50)	13/21 (62)	37/70 (53)	.3
Human immunodeficiency virus (%)	0/47 (0)	2/21 (10)	2/68 (3)	.1
History of previous cancer (%)	34/49 (69)	3/21 (14)	37/70 (53)	<.0001
History of autoimmune disease (%)	6/49 (12)	8/20 (40)	14/69 (20)	.009
Immunocompromised (%)	31/43 (71)	10/19 (53)	41/62 (66)	.16

Abbreviations: NM, neoplastic meningitis; NNM, non-neoplastic meningitis.

^a Bonferroni corrected $\alpha = 0.01$.

enhancement unrelated to chronic or subacute meningitis (eg, secondary to meningiomas, venous sinus thrombosis, epidural or subdural hematomas, and intracranial hypotension) were excluded. Brain 3 T or 1.5 T MRI was performed in all patients, and spine MRI was performed in patients with spinal symptoms or when oncologic screening was required. Both chronic and subacute pachymeningitis (dura and arachnoid mater) and leptomeningitis (arachnoid and pia mater) were included. Leptomeningeal nodular enhancement was defined as multiple small lesions in the leptomeningeal space. Each MRI was analyzed by a neuroradiologist as part of routine clinical care.

Chronic and subacute meningitis patients without MRI meningeal enhancement diagnosed by clinical and CSF abnormalities were included. Cerebrospinal fluid values were considered normal if leucocyte count was <5 cell/mm³, CSF-to-serum glucose ratio was >0.6 , and CSF protein concentration was <45 mg/dL. Cerebrospinal fluid was cultured for bacteria, fungi, and mycobacteria; viral and mycobacterial polymerase chain reaction (PCR) was performed. Cerebrospinal fluid adenosine deaminase, fungal antigens, and antibodies were assayed. Serum specific tests performed on all NNM patients included angiotensin converting enzyme, antinuclear, anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, and immunoglobulin G4 (IgG4). Oncologic screening with full-body computed tomography was performed in all patients, and biopsies were obtained when a primary tumor was identified. Meningeal (dural and leptomeningeal) brain biopsy was only performed when no diagnosis could be established.

Previous cancer was defined as a history of cancer within the last 5 years. Meningeal TB was diagnosed by positive CSF cultures or PCR. Those cases suspected of TB, but without CSF confirmation by the mentioned methods, were categorized as idiopathic meningitis. Fungal meningitis was confirmed with CSF cultures or CSF fungal antigen in the case of *Cryptococcus neoformans*.

Vogt-Koyanagi-Harada¹⁷ and IgG4-related meningitis diagnoses were achieved by fulfilling diagnostic criteria or

meningeal biopsy, respectively. Neoplastic cases were diagnosed by positive CSF cytology or meningeal biopsy.

Cases of CSM with a negative workup, including 3 separate CSF cytology samples and negative systemic oncologic screening, were considered "idiopathic" and were followed for at least 1 year.

Normally distributed variables are reported as mean (standard deviation). Non-parametrically distributed variables are reported as median and range. Comparison between neoplastic and non-neoplastic cases was performed according to parametric (Student *t*-test) and nonparametric (Mann-Whitney *U* test) variable distribution. Categorical variables were analyzed with χ^2 or Fisher exact test. Bonferroni corrected *P* values were considered significant less than .001 in demographic variables, .004 in physical examination findings, and .01 in diagnostic test results. Data were analyzed using Stata v12.1 (StataCorp, College Station, Texas). The study was approved by the Institutional Ethics Committee, and a waiver of informed consent was granted.

Results

Seventy patients with CSM were included. Median age was 56.5 years (range: 18-81 years). Forty-nine cases had neoplastic meningitis (male:female [M:F] = 1:1.5), and 21 had non-neoplastic meningitis (M: F = 1:1.25). No statistically significant differences between age at diagnosis, sex, tobacco use, or human immunodeficiency virus were found between groups. History of cancer was significantly higher in neoplastic than non-neoplastic cases (69% vs 14%, $P < .0001$), with median time from primary cancer diagnosis to meningeal carcinomatosis diagnosis of 26 months (range: 1-276). Autoimmune disease prevalence was more frequent in NNM vs NM (40% vs 12%, $P = .009$) either as a CSM cause (rheumatoid arthritis: $n = 2$, IgG4-related diseases: $n = 2$, and Sjogren syndrome: $n = 2$) or by predisposing to infections due to immunosuppression (neuromyelitis optica: $n = 1$). Other autoimmune diseases in which a clear correlation with meningitis could not be explained were Hashimoto thyroiditis and/or vitiligo (Table 1).

Table 2. Relevant Findings on Physical Examination.

	NM (%)	NNM (%)	All Patients (70)	P Value ^a
Headache	32/49 (65)	14/21 (67)	46/70 (66)	.9
Intracranial hypertension	21/48 (44)	8/20 (40)	29/68 (43)	.8
Fever	3/49 (6)	12/21 (57)	15/70 (21)	<.0001
Meningeal signs	20/49 (41)	10/21 (48)	30/70 (43)	.6
Psychiatric symptoms ^b	8/49 (16)	2/21 (10)	10/70 (14)	.5
Cognitive decline	11/48 (23)	4/21 (19)	15/69 (22)	.7
Sensory impairment	12/49 (24)	6/21 (29)	18/70 (26)	.7
Seizures	11/49 (22)	4/21 (19)	15/70 (21)	.7
Pyramidal signs	20/48 (42)	7/21 (33)	27/69 (39)	.5
Aphasia	9/48 (19)	4/21 (19)	13/69 (19)	.1
Sensitive symptoms ^c	8/49 (16)	3/21 (14)	11/70 (16)	.8
Spinal compromise	6/49 (12)	2/21 (10)	8/70 (11)	.7
Ataxia	9/49 (18)	3/21 (14)	12/70 (17)	.7
I	1/49 (2)	0/21 (0)	1/70 (1)	.5
II	9/49 (18)	3/21 (14)	12/70 (17)	.7
III	11/49 (22)	5/21 (24)	16/70 (23)	.9
IV	5/49 (10)	0/21 (0)	5/70 (7)	.3
V	7/49 (14)	1/21 (5)	8/70 (11)	.4
VI	18/49 (37)	5/21 (24)	23/70 (33)	.3
VII	16/49 (33)	5/21 (24)	21/70 (30)	.5
VIII	17/49 (35)	6/21 (29)	23/70 (33)	.6
IX	6/49 (12)	2/21 (10)	8/70 (11)	.1
X	8/49 (16)	0/21 (0)	8/70 (11)	.1
XI	1/48 (2)	0/21 (0)	1/69 (1)	.1
XII	2/49 (4)	0/21 (0)	2/70 (3)	.1
Constitutional syndrome ^d	27/49 (55)	8/21 (38)	35/70 (50)	.2
Extra-neurological symptoms ^e	3/33 (9)	7/19 (37)	10/52 (19)	.03

Abbreviations: NM, neoplastic meningitis; NNM, non-neoplastic meningitis.

^aBonferroni corrected $\alpha = .004$.

^bPsychiatric symptoms: confusion, behavioral changes, agitation, hallucinations, and depression.

^cSensitive symptoms: hypoesthesia or paresthesia.

^dConstitutional syndrome: weight-loss, hypophagia, and asthenia.

^ePneumonia, asthma, cough, dacryoadenitis, SICCA syndrome. I to XII: cranial nerves. I: olfactory, II: optic, III: oculomotor nerve, IV: trochlear, V: trigeminal, VI: abducens, VII: facial, VIII: vestibulocochlear, IX: glossopharyngeal, X: vagus, XI: accessory, and XII: hypoglossal.

Fever was the only clinical manifestation significantly different between the groups (NM 6% vs NNM 57%, $P < .0001$). Extra-neurological symptoms such as cough, pneumonia, asthma, dacryoadenitis, and hypopituitarism were more common in NNM (37% vs 9%, $P = .03$). Seizures, cognitive or speech impairment, ataxia, cranial nerve involvement, and other symptoms analyzed were similar between groups (Table 2).

Laboratory findings (Table 3) showed a trend toward higher C-reactive protein levels in NNM (34.2 mg/L, range: 0.5-247 mg/L vs 6.6 mg/L, range: 0.5-122.4 mg/L; $P = .05$) as well as CSF pleocytosis (median: 20 cell/mm³, range: 0-780 cell/mm³ vs median: 5 cell/mm³, range: 0-585 cell/mm³; $P = .04$). An equal proportion of cases in both groups

showed neutrophil predominance in the CSF (NM = 20% vs NNM = 19.4%). Overall, cytology was positive in 66.6% of NM cases ($n = 26$): 16 resulted positive after the first lumbar puncture, 5 after the second, and 3 after a third test. Two patients required a cisternal tap to achieve a positive cytology. In some cases, meningeal brain biopsy ($n = 18$) was necessary to confirm diagnosis.

Leptomeningeal enhancement on MRI was suggestive of NM (65.5% vs 26%, $P = .009$) as was a nodular enhancement pattern (46% vs 11%, $P = .008$). In the 9 cases of neoplastic isolated pachymeningitis, 3 were due to lung cancer, 3 due to breast cancer, 2 due to lymphoma, and 1 due to melanoma (Figure 1).

The most frequent causes of NM were secondary spread of breast or lung cancer (30.6% and 28.5%). Idiopathic, TB, and fungal meningitis (*C neoformans*, $n = 2$; *Histoplasma capsulatum*, $n = 1$; and *Aspergillus fumigatus*, $n = 1$) were the most common diagnoses in the NNM group (42.8%, 19%, and 19%; Table 4). Death during follow-up was more frequent in the NM group (71% vs 15%, $P < .001$).

Conclusions

Chronic and subacute meningitis represents a challenge in daily neurological practice. As illustrated in this single center case series from Buenos Aires, causative etiologies are often rare, complex diseases, for which many diagnostic tests need to be performed and for which treatment options are highly variable.

In line with other authors,² we believe a complete clinical history is essential to orient diagnostic testing as evidenced by specific details that distinguished NM from NNM in our case series. Cancer history strongly suggests NM, and extra-neurological symptoms strongly suggest a systemic inflammatory background, especially when dacryoadenitis, hypophysitis, serositis, or fever is present. Neoplastic meningitis is more frequently seen in progressive disseminated oncologic disease. A higher percent of patients (31%) presented CSM as their debut symptom compared to other published series (5%-10%),¹⁸ suggesting the need for improving regional oncologic screening and referral for treatment.

Autoimmunity or rheumatology-related testing is useful when common pathophysiologic mechanisms or infectious susceptibility secondary to immunosuppression is suspected.^{8,19-21} While precise data are scarce, published evidence suggests that Sjogren syndrome, rheumatoid arthritis, giant cell arteritis, Behçet, ANCA, and IgG4-related diseases may cause CSM.²²⁻²⁴ Because CSM prevalence is low, exact figures regarding central nervous system (CNS) involvement by systemic diseases remain uncertain. Even with a complete work-up, many cases remained idiopathic in our series. Once infectious etiologies are ruled out, immunosuppression could be proposed with uncertain benefits.

Statistically significant differences in favor of fever-accompanying NNM could probably be explained by the low

Table 3. Diagnostic Tests Performed in CSM Patients.

	NM	NNM	All Patients	P Value ^a
Laboratory results				
ESR, (median, range, mm/h)	50 (5-120)	48.5 mm/h (7-120)	50 (5-120)	.9
CRP (median, range, mg/L)	6.6 mg/L (0.5-122.4)	34.2 mg/L (0.5-247)	12 (0.5-247)	.05
Lumbar puncture				
Opening pressure (median, range, cmH ₂ O)	18 cmH ₂ O (3.5-100)	16 H ₂ O (6-36)	18 (3.5-100)	.2
Cells (median, range, mm ³)	5/mm ³ (0-585)	20/mm ³ (0-780)	12 (0-780)	.04
Glycorrachia (median, range, mg/dL)	53.5 (7-192)	40 (16-70)	49 (7-192)	.2
Elevated CSF proteins (%)	33/39 (85)	19/21 (90)	52/60 (87)	.7
Positive cytology (%) ^b	26/39 (66.6)	2/21 (10)	20/60 (53)	<.0001
Magnetic resonance imaging				
Normal (%)	9/47 (19)	4/21 (19)	55/68 (81)	.9
Leptomeningeal enhancement (%)	25/40 (62.5)	5/19 (26)	30/59 (51)	.009
Pachymeningeal enhancement (%)	13/40 (32.5)	10/19 (53)	23/59 (39)	.1
Focal enhancement (%)	21/42 (50)	9/20 (45)	30/62 (48)	.4
Nodular enhancement pattern (%)	19/41 (46)	2/19 (11)	21/60 (35)	.008
Homogeneous enhancement pattern (%)	21/40 (52.5)	12/19 (63)	33/59 (56)	.4
Associated intraparenchymal lesions (%) ^c	24/43 (56)	7/20 (35)	31/63 (49)	.1

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; NM, neoplastic meningitis; NNM, non-neoplastic meningitis.

^aBonferroni corrected $\alpha = 0.01$.

^bTwo positive cytologies in NNM group were considered false positive after reconfirming with repeat cerebrospinal fluid findings.

^cIntraparenchymal lesions: tumor in case of NM, and different parenchymal lesions in NNM, from associated vasculitis in tuberculosis cases, cryptococcomas in cryptococcal meningitis, and hypophysitis enhancement in IgG4-related meningitis.

Figure 1. A, Idiopathic hypertrophic focal pachymeningitis. B, Leptomeningitis secondary to small cell lung cancer. C, Idiopathic pachymeningitis. D, Basal skull tuberculous meningitis. E, Immunoglobulin (Ig) G4-related dacryoadenitis. F, Tuberculous leptomeningitis. G, Tuberculous pachymeningitis. H, Basal ganglia cryptococcosis. I, Idiopathic pachymeningitis. J, Pachymeningitis secondary to breast cancer.

prevalence of meningeal lymphomatosis in this series and the proportionally higher incidence of infectious diseases (eg, TB and fungal meningitis). Although fever when present will orient diagnosis to NNM, NM cannot be ruled out, since multiple neoplastic diseases can produce fever.

Spinal tap can contribute to diagnosis. A pleocytosis suggests NNM, while the differential on CSF cell count does not bring specific diagnostic information; cytology often leads to diagnosis in NM. We observed higher positive CSF cytology than other published series.^{18,25} With adequate CSF volume

Table 4. Chronic and Subacute Meningitis Diagnosis.

Diagnosis	Number of Patients (%)
Neoplastic meningitis primary tumor sites	
Breast cancer	15 (30.6)
Lung cancer	14 (28.5)
Meningeal lymphomatosis	4 (8.1)
Unknown primary	3 (6.1)
Prostate cancer	2 (4)
Nasopharyngeal cancer	2 (4)
Meningeal primary neuroectodermal tumor (PNET)	2 (4)
Melanoma	2 (4)
Endometrial cancer	1 (2)
Oligodendroglioma	1 (2)
Neurocutaneous melanosis	1 (2)
Urachal carcinoma	1 (2)
Medulloblastoma	1 (2)
Non-neoplastic meningitis	
Idiopathic meningitis	9 (42.8)
TB meningitis	4 (19)
Fungal meningitis ^a	4 (19)
IgG4-related meningitis	2 (9.5)
Vogt-Koyanagi-Harada syndrome	1 (4.7)
Postprocedural meningitis	1 (4.7)

Abbreviation: Ig, immunoglobulin; TB, tuberculosis.

^a*Cryptococcus neoformans*: n = 2, *Histoplasma capsulatum*: n = 1, *Aspergillus fumigatus*: n = 1.

(at least 10.5 mL) and processing time, reported test sensitivity is 50%, increasing to 75% after a second test. If NM is still suspected after repeated negative CSF analysis, cisternal puncture or meningeal biopsy may be considered after assessing risk-benefit balance. Cerebrospinal fluid TB PCR should be performed in all patients with suspected NNM. However, because test sensitivity varies (65%-83%),²⁶ CSF adenosine deaminase analysis is mandatory when TB PCR results are negative; activity levels surpassing 8-10 UI/L suggest meningeal tuberculosis.⁵ Although definitive TB diagnosis is only established by mycobacterium-positive smear or culture,²⁷ antituberculous treatment should be initiated promptly given disease severity and potential complications. In parallel, CSF cultures, antigens, and antibodies for fungal infections should be investigated based on local prevalence.

Most authors report pachymeningeal enhancement as present only in NNM.²⁸ However, a considerable number of NM cases in this series, particularly those secondary to breast cancer, showed pachymeningeal involvement, a point to consider during oncologic screening, especially in middle-age women with CSM. Also noteworthy was the fact that the vast majority of non-neoplastic pachymeningitis cases in this series were idiopathic despite extensive diagnostic testing, including dural brain biopsy, IgG4, ANCA, and rheumatoid arthritis investigations. As previously reported, a nodular pattern of leptomeningeal enhancement predicted neoplasm.^{18,29} We also observed more frequent leptomeningeal involvement in

infectious NNM than in inflammatory NNM (Table 3). We consider this point of special interest. Leptomenigitis of infectious origin still needs to be ruled out even if cancer is suspected, particularly in patients presenting with fever, which can develop after chemotherapy, or in patients receiving immune suppressants.

Etiologies diagnosed in this CSM case series probably present selection bias because our institution is a tertiary neurological referral center, and most prevalent infectious or systemic diseases such as sarcoidosis will be treated in primary, secondary, or general care centers.

As expected, death rate was higher in patients with NM, which is a frequent complication of advanced stage cancer, with poor prognosis and increased mortality, even after intrathecal chemotherapy.^{14,30,31} Improved CNS imaging and treatment strategies have increased detection rates and prolonged survival of NM, but outcomes are still poor with median survival rates of 4 to 6 weeks for untreated patients and up to 6 months with more aggressive treatment.³²

Non neo-plastic meningitis cases were idiopathic (unknown cause) in a significant percentage (42.8%). However, idiopathic cases could still be neoplastic even after a year of close follow-up with repetitive CSF cytologies, representing the diagnostic challenge in this group of patients.

We conclude that, when a patient presents with CSM, complete medical history and specific diagnostic testing are needed to achieve prompt diagnosis for treatable causes and to provide adequate information on therapeutic strategies and prognosis to patients and families. A diagnosis can be found in a majority of cases.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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