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Characteristics and outcome of spontaneous bacterial meningitis in patients with cancer compared to patients without cancer

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Abstract

In cancer patients, who are frequently immunocompromised, bacterial meningitis (BM) can be a severe complication, with a different presentation, etiology, and course, compared to patients without cancer. Our objective is to compare the characteristics and outcomes of BM in patients with and without cancer. A single-center, prospective observational cohort study, conducted between 1982 and 2012, in a tertiary university hospital in Barcelona (Spain). The main outcome measure is in-hospital mortality. We evaluated 659 episodes of BM; 97 (15%) had active cancer. Patients with malignancies were older (median 63 (interquartile range [IQR] 24) vs 52 [IQR 42] years, $P < .001$) and more often had a Charlson comorbidity score of ≥3 (51% vs 11%, $P < .001$). The classic meningitis triad (35% vs 50%, $P = .05$), fever (91% vs 96%, $P = .03$), neck stiffness (58% vs 78%, $P < .001$), headache (63% vs 77%) $P = .003$), and rash (7% vs 30%, $P < .001$) were less frequent. There was a longer interval between admission and antibiotic therapy (median 5 [IQR 14] vs 3 [IQR 6] hours, $P < .001$). Listeria meningitis was the commonest cause of BM (29%) and was more frequent in cancer than noncancer (8%, $P < .001$) patients, whereas meningococcal meningitis was much less frequent (4% vs 36%, $P < .001$). Overall mortality was higher in patients with cancer (31% vs 16%, $P < .001$), although cancer was not associated with an unfavorable outcome in the multivariate analysis (odds ratio 1.825, $P = .07$). Patients with meningitis and cancer are older and have more subtle clinical manifestations than patients without cancer. *Listeria monocytogenes* is the predominant pathogen and mortality is higher in cancer patients.

Abbreviations: ATI = admission-therapy interval, BM = bacterial meningitis, CLSI = Clinical Laboratory Standards Institute, CSF = cerebrospinal fluid, CT = computed tomography, IQR = interquartile range, LP = lumbar puncture, SPSS = Statistical Product and Service Solutions.

Keywords: bacterial infection of the central nervous system, bacterial meningitis, cancer, spontaneous meningitis

1. Introduction

Bacterial meningitis (BM) is one of the main causes of infection-related death worldwide.[1,2] The relative prevalence of BM varies with the years and according to time of year, geography and the age of the patient. In developed countries, the estimated incidence is 4 to 6 cases per 100,000 adults per year, and the most frequent causative agents in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*.[1–6]

Cancer is a significant cause of morbidity, and its incidence tends to increase with age. Compared to patients without malignancies, the presentation and course of common infections in cancer patients may vary, leading to possible delays in diagnosis.[7] BM can be a severe complication in cancer patients, who are likely to be more susceptible to meningeal pathogens for reasons such as the use of immunosuppressive chemotherapy, indwelling vascular catheters, and head and neck surgery. The true incidence of spontaneous BM in these patients is not known with certainty since most previous reports have combined spontaneous meningitis with meningitis secondary to neurosurgical procedures. We observed in previous studies that adults with BM had underlying malignancies in 15% of cases; furthermore there was a higher frequency in more recent years (8% during the period 1982–1995; 21% during 1996–2010) and among older patients (11% in the nonelderly; 19% in ≥65 years).[4,8]

The causative organisms may differ from those identified in the general population, depending on the type of immunodeficiency,

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Key message: Cancer is a significant cause of morbidity, and its incidence tends to increase with age. Spontaneous bacterial meningitis is one of the main causes of infection-related death worldwide. Our objective is to compare the characteristics and outcomes of bacterial meningitis in patients with and without cancer during 31-year period (1982–2012). This knowledge may improve the medical management of these patients, their prognosis and their mortality.

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local nosocomial trends, and specific vulnerabilities created by the underlying disease and treatment regimen.[9]

Nonetheless, there are few studies about the characteristics and outcomes of spontaneous BM in patients with cancer. Most of them were published more than a decade ago although recently, a study of patients with active cancer or a history of cancer and with community-acquired meningitis has been published.[7,9–11] Epidemiology, treatments and outcomes could have changed in recent years.

Using data from a large, single-center prospective study of patients of 14 years or more diagnosed with spontaneous BM over a 31-year period (from 1982 to 2012), we compared the prevalence, etiology, clinical characteristics, and outcome of spontaneous BM in adults with cancer with those in patients without malignancies.

2. Patients and methods

2.1. Setting and study population

We used data from a large, single-center prospective cohort of patients with meningitis, enrolled over a 31-year period at the Hospital de la Santa Creu i Sant Pau (Barcelona, Spain), a 540-bed tertiary university hospital serving an estimated population of 410,500 in a predominantly urban area.

From 1982 through 2012, all consecutive adults (defined as patients of 14 years old or more) with a diagnosis of acute BM at the Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) were prospectively identified and followed. The characteristics of this cohort have been described previously.[4,8,12] From 1999, information about the results of cerebral computed tomography (CT) scans, diagnostic sequence of CT in relation to lumbar puncture (LP), and start of antibiotic treatment were also registered.

Data were collected during the index hospitalization, and the patient was followed after discharge by one of the authors (PD or VP). Follow-up always included a neurological examination, neuropsychological testing, complement and immunoglobulin levels, and audiometry.

The study and its subsequent amendments were approved by the ethics committee of the Hospital de la Santa Creu i Sant Pau.

2.2. Diagnosis of acute bacterial meningitis

A diagnosis of meningitis caused by a specific bacterial pathogen was based on compatible clinical findings (sudden onset of headache, fever, nausea, vomiting, neck stiffness, and/or altered mental status) and one of the following: a positive cerebrospinal fluid (CSF) culture or a negative CSF culture showing neutrophilic pleocytosis (defined as pleocytosis of at least 100 neutrophils per cubic millimeter), and at least one of the following: a positive CSF antigen test, a positive blood culture, or Gram-negative diplococci identified on a CSF Gram stain from patients with a petechial or purpuric rash and a fulminant course (the latter cases were considered to be caused by *N. meningitidis*).[13] Episodes of acute BM without an etiological diagnosis were also included if the patient had a compatible clinical picture together with neutrophilic pleocytosis and any of the following CSF abnormalities: depressed CSF glucose (defined as a CSF to blood glucose ratio of <0.40) and elevated CSF protein levels (defined as >0.5 g/L).[3,6,14]

Cases of viral, fungal, or mycobacterial meningitis were not included.

Patients with a history of neurosurgical procedures or traumatic head/spinal injuries were excluded.

2.3. Microbiology methods

Isolates were obtained from routine cultures and identified using standard methods.[15]The disc diffusion susceptibility test was performed according to Clinical Laboratory Standards Institute (CLSI) guidelines,[16] using commercially available discs (Bio-Rad, Marnes La Coquette, France). Minimal inhibitory concentrations were determined by the broth microdilution method, according to CLSI guidelines,[17] using commercial panels (Sensitre, Trek diagnostic systems, West Sussex, England) or Etest (AB Biodisk, Solna, Sweden), according to the manufacturers' recommendations.

2.4. Definitions

The Charlson Comorbidity Index was used to assess *comorbidity*.[18,19]

Active cancer included solid and hematologic malignancies according to histopathological or cytological evidence treated during the previous 5 years but excluded nonmelanoma skin cancer and in situ cervical cancer.[18]

Communication of the subarachnoid space with the skin, sinuses, or mucosal surfaces, and upper respiratory tract infection (frequent in meningococcal disease) were not considered distant foci of infection.[20]

The interval, in hours, between onset of signs and symptoms of BM and admission to hospital was the *symptoms-admission interval*. When the onset of symptoms could not be precisely determined, onset of illness was assumed to be the mean interval between the last time the patient was asymptomatic, as observed by a household member, and the first time the patient was seen ill.[21]

The interval, in hours, between hospital admission and first dose of antibiotics for the treatment of meningitis was the *admission-therapy interval* (ATI).

Coma was defined as a score of 6 or less on the Glasgow Coma Scale in the absence of sedation.[22]

Adequate antibiotic treatment was defined as the intravenous administration of any antimicrobial agents to which isolated bacteria were sensitive following susceptibility testing at local laboratories, crossed the blood–brain barrier in adequate amounts, was administered in a dose recommended for acute BM and commenced on the day of admission or before deterioration of neurological and systemic conditions in inpatients.[20,23,24]

Dexamethasone therapy was only considered when a first dose of dexamethasone of at least 10 mg/24 hours was administered before or concomitant with the first antibiotic dose. Steroids administered after starting antibiotic therapy were not considered.[25]

Nosocomial meningitis was defined as developing more than 48 hours after admission or within 1 week of discharge.[26]

Mortality was evaluated during the hospitalization. Meningitis was not considered to be the underlying or immediate cause of death if a disease process unrelated to meningitis began >24 hours after meningitis resolution and initiated the train of morbid events leading directly to death.[27,28]

Sequelae were defined as any disability, disorder, or injury demonstrated during hospital stay or upon discharge from hospital that was not present before the episode of BM and persisted at 6 months after discharge.[28]

Other definitions are described in previous articles.[4,8,12]

Table 1

Demographics and clinical features of spontaneous bacterial meningitis episodes.

Characteristics[‡]	Cancer patients (n = 97)	Other patients (n = 561)	*P*
Male sex	59/97 (60.8)	260/561 (46.3)	.008
Age, y, median (IQR)	63 (24)	52 (42)	<.001
Recurrent meningitis	4/97 (4.1)	23/561 (4.1)	.991
Comorbid conditions[*]	97/97 (100)	246/561 (43.9)	<.001
Hypertension	14/97 (14.4)	42/561 (7.5)	.024
Diabetes mellitus	11/97 (11.3)	80/561 (14.3)	.442
Alcoholism	8/97 (8.2)	58/561 (10.3)	.527
Chronic lung disease[†]	7/97 (7.2)	30/561 (5.3)	.461
Charlson comorbidity index ≥3	50/97 (51.5)	60/561 (10.7)	<.001
Distant focus of infection	34/97 (35.1)	190/561 (33.9)	.820
Route of acquisition			
Hospital-acquired (vs community-acquired)	15/97 (15.5)	15/561 (2.7)	<.001
Symptoms on presentation			
Fever	88/97 (90.7)	537/561 (95.7)	.037
Altered mental status	62/97 (63.9)	363/561 (64.7)	.881
Neck stiffness	56/97 (57.7)	439/561 (78.3)	<.001
Triad of fever, neck stiffness, and change in mental status	34/97 (35.1)	278/561 (49.6)	.051
Headache	61/97 (62.9)	433/561 (77.2)	.003
Nausea and/or vomiting	29/97 (29.9)	329/555 (58.6)	<.001
Focal neurological deficits	22/97 (22.7)	91/561 (16.2)	.119
Coma	23/97 (23.7)	85/561 (15.2)	.102
Seizures	8/97 (8.2)	44/561 (7.8)	.892
Rash	7/97 (7.2)	166/561 (29.6)	<.001
Systolic blood pressure, mm Hg (SD)	132 (27)	125 (31)	.007
Diastolic blood pressure, mm Hg (SD)	77 (16)	75 (20)	.612
Interval symptoms-admission, h (IQR)	36 (45.5)	24 (24)	.682
Interval admission-therapy, h (IQR)	5 (14)	3 (6)	<.001
Prior antimicrobial therapy	36/97 (37.1)	170/561 (30.3)	.182
Cerebral computed tomography	49/97 (50.5)	137/561 (24.4)	<.001

[*] Patients may have more than 1 comorbid condition. CI = confidence interval.

[†] Includes: chronic bronchitis (27), asthma (5), idiopathic pulmonary fibrosis (2), other pneumopathies (3). IQR = interquartile range, SD = standard deviation.

[‡] Values are reported as no./no. evaluated (%), unless otherwise noted.

2.5. Statistical analysis

Qualitative variables were summarized using absolute numbers and percentages and quantitative variables with means and standard deviation or medians and interquartile range (IQR) (depending on homogeneity).

Continuous variables were compared using the Student *t* test or Mann–Whitney *U* test, as appropriate. Categorical data were analyzed using the χ^2 test or Fisher exact test, as indicated.

Logistic regression was used to calculate adjusted odds ratios and determine whether mortality differed between the 2 groups, with adjustment for clinically relevant covariates. Nagelkerke R^2 was used to assess the proportion of the total variation of outcomes explained by the model.

All statistical tests were 2-tailed, and a *P* value of <.05 was considered to be statistically significant. Statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) software, version 19 (SPSS Inc, Chicago, IL).

3. Results

A total of 659 episodes of spontaneous acute BM were diagnosed during the 31-year study period; 632 patients had a single episode of meningitis, and 18 patients had more than 1. Forty-eight percent of patients were male, with a median age of 54 years for the meningitis episodes (IQR 39). Etiology was established in 531 cases (80.6%). *N. meningitidis* was the most common microorganism overall, accounting for 31.1% of episodes; *S. pneumoniae* caused 23.7%, whereas Gram-negative bacilli other than *Haemophilus influenzae and Listeria monocytogenes* accounted for 10.9% and 5.6%, respectively.

Of these 659 episodes, 97 (15%) occurred in patients with active cancer: 28 (4%) between January 1982 and June 1997, and 69 (11%) between July 1997 and December 2012 ($P < .001$).

3.1. Characteristics of spontaneous bacterial meningitis in patients with cancer

Of the primary cancer types represented, 24% were intracranial or head and neck (23 cases), 37% hematologic malignancies (36 cases), and 36% (35 cases) involved other solid tumors (Supplementary table 1, http://links.lww.com/MD/B696). One patient had both solid and hematologic malignancies.

The demographic characteristics of the population are summarized in Table 1. Patients with cancer were older and more likely than patients without cancer to have a Charlson comorbidity score of ≥3 and hospital-acquired meningitis. However, when the Charlson comorbidity score was recalculated, excluding cancer and metastases, the comorbidity score for the 2 groups was similar (Charlson comorbidity index ≥3 was 8/97 [8%] in cancer patients versus 52/561 [9%], $P = .763$).

Episodes of BM in patients with cancer were significantly more likely to be hospital-acquired than were episodes of noncancer patients.

There was a higher, although not statistically significant, probability of patients with cancer having received out-of-

Table 2

CSF findings, microbiologic features and etiology of bacterial meningitis.

Characteristics[||]	Cancer patients (n = 97)	Other patients (n = 561)	*P*
CSF examination			
White blood cell count, median (IQR)	658 (2273)	1120 (2865)	.248
Protein, g/L, median (IQR)	2.90 (3.83)	3.39 (5.10)	.705
CSF/plasma glucose ratio, median (IQR)	0.24 (0.35)	0.24 (0.37)	.795
Positive CSF Gram-stained smear	25/97 (25.8)	246/561 (43.9)	.004
Positive CSF culture	65/97 (67.0)	402/561 (71.7)	.464
Positive blood culture	50/97 (51.5)	246/561 (43.9)	.267
Etiology			
Meningococcal	4/97 (4.1)	200/561 (35.7)	<.001
Pneumococcal	21/97 (21.6)	135/561 (24.1)	.606
Listeria and Gram-positive bacilli[*]	28/97 (28.9)	44/561 (7.8)	<.001
Gram-negative bacilli[†]	8/97 (8.2)	31/561 (5.5)	.295
Haemophilus influenza	1/97 (1.0)	14/561 (2.5)	.372
Other[‡]	9/97 (9.3)	31/561 (5.5)	.153
Mixed[§]	2/97 (2.1)	2/561 (0.4)	.046
Unknown origin	24/97 (24.7)	104/561 (18.5)	.154
White blood cell count, median (IQR)	13,100 (12100)	15,800 (10700)	.005
Thrombocyte platelets count/μL, median (IQR)	179,000 (165000)	1975,000 (113750)	.495

CI = confidence interval, IQR = interquartile range, SD = standard deviation; CSF = cerebrospinal fluid.

Gram-positive bacilli[*]: *Listeria monocytogenes* (68) and Bacillus spp. (4). Gram-negative bacilli[†]: *Escherichia coli* (17), *Pseudomonas aeruginosa* (8), *Pseudomonas* spp (3), *Klebsiella* spp (2), *Proteus mirabilis* (2), *Serratia marcescens* (1), *Serratia* spp (2), *Enterobacter cloacae* (1), *Citrobacter freundii* (1), *Bacteroides melaninogenicus* (1), *Acinetobacter baumannii* (1). Other[‡]: *Brucella* spp (2), *Neisseria subflava* (1). Mixed meningitis[§]: *Bacteroides intermedius* + *Streptococcus viridans* (1), *E. cloacae* + *S. viridans* (1), *Peptostreptococcus* spp + anaerobic unidentified Gram-negative bacilli (1), and *Peptostreptococcus* spp + *Bacteroides* spp (1).

[||]Values are reported as no./no. evaluated (%), unless otherwise noted.

hospital antibiotic therapy. Although the time interval between first symptoms and arrival at the hospital was similar for both patient groups, patients with malignancies experienced a greater delay between arrival at the hospital and start of antibiotic therapy. The fever, as well as neck stiffness, headache, nausea, and rash were less frequent among patients with cancer than those without.

3.2. Diagnosis and microbiology

LP was performed on all patients and the CSF showed at least 1 CSF finding suggestive of acute BM: increased protein levels in 91 cases (94%), a decreased CSF glucose/blood glucose ratio in 83 cases (86%), and pleocytosis with an elevated neutrophil count in 88 cases (91%) (Table 2). CSF cytobiochemical findings did not differ significantly between the 2 groups of patients, although patients with cancer had a lower diagnostic yield for the CSF Gram-stained smears. Blood cultures were more frequently positive in cancer patients, although the difference was not statistically significant.

Patients with cancer presented with lower white blood cell count (Table 2) and CT brain scan was performed on admission more frequently than in patients without cancer (Table 1).

In patients with cancer, the most common organisms during the study were *L. monocytogenes* (29% vs 7.8% in noncancer patients, $P < .001$), followed by *S. pneumoniae* (22% vs 24%, $P = .606$). There were only 4 (4.1%) out of 97 cases with meningococcal meningitis, and *N. meningitidis* was the most frequent cause of meningitis in patients without cancer (36%, $P < .001$). This etiology did not vary between the 2 periods of study.

3.3. Treatment

Initial empirical antibiotic treatment was appropriate in 82 patients with cancer (84%), which was less frequent than for noncancer patients (94%, $P < .001$) (Table 3). Nine of 28 (32%) meningitis caused by *L. monocytogenes* did not receive treatment in compliance with the guidelines (vs 5/69 [7%] $P = .002$).

The median duration of antibiotic treatment was 16 days (IQR 11).

There were no differences between the 2 groups in the administration of adjunctive steroids before or with the first dose of antibiotic treatment (44% vs 34%).

3.4. Outcome

There were no statistically significant differences between groups with respect to neurological and systemic complications. Patients with malignancies however were more likely to have neurological complications (27% vs 22%, $P = .056$) but developed fewer sequelae after the meningitis episode (6% vs 11%, $P < .001$).

The overall mortality rate was significantly higher in patients with cancer (31% vs 16%, $P < .001$) (Table 4) with no differences in the 2 periods (8 until June 1997 [27%], 22 between July 1997 and December 2012 [73%], $P = .813$). However, in the multivariate analysis, after adjusting for relevant clinical variables, cancer was not associated with an unfavorable outcome (Table 4).

3.5. Characteristics of BM between solid and hematologic malignancies

After comparing the clinical features, etiology and outcomes of patients with hematologic malignancies and those with solid tumors, no significant differences were found (Supplementary table 2, http://links.lww.com/MD/B696).

4. Discussion

The increased survival of cancer patients treated with aggressive radiation and chemotherapy regimens has led to a diverse range

Table 3

Evolving features and outcome of bacterial meningitis.

Characteristics*	Cancer patients (n = 97)	Other patients (n = 561)	P
Neurological complications	26/97 (26.8)	123/561 (21.9)	.056
Impaired mental status	23/97 (23.7)	86/561 (15.2)	.040
Seizures	17/97 (17.5)	64/561 (11.2)	.090
Cranial palsies	6/97 (6.2)	29/561 (5.2)	.680
Focal neurological deficits	3/97 (3.1)	17/561 (3.0)	.974
Systemic complications	36/97 (37.1)	176/561 (31.4)	.131
Acute respiratory failure	19/97 (19.6)	96/561 (17.1)	.553
Acute kidney injury	15/97 (15.5)	78/561 (13.9)	.684
Septic shock	13/97 (13.4)	88/651 (15.7)	.564
Disseminated intravascular coagulation	5/97 (5.2)	51/561 (9.1)	.302
Therapeutics			
Adequate empiric antibiotic therapy	82/97 (84.5)	525/561 (93.6)	<.001
Dexamethasone therapy	43/97 (44.3)	189/561 (33.7)	.121
Vasoactive drugs	9/97 (9.3)	80/561 (14.3)	.185
Mechanical ventilation	11/97 (11.3)	84/561 (15)	.586
Dialysis	2/97 (2.1)	16/561 (2.9)	.831
Outcome			
Neurological sequelae	6/97 (6.2)	63/561 (11.2)	<.001
In-hospital mortality	30/97 (30.9)	89/561 (15.9)	<.001

CI = confidence interval, IQR = interquartile range, SD = standard deviation.
*Values are reported as no./no. evaluated (%), unless otherwise noted.

of complications, among which infections of the central nervous system play a significant part, resulting in prolonged hospitalization, extensive diagnostic tests, and high mortality.[29] More unusual opportunistic pathogens can cause infection and the presentation and course of common infections in cancer patients may also be different from those in patients without malignancies, which may delay accurate diagnosis.[7,30,31]

Our study showed an increased frequency of BM in patients with cancer over the 31-year study period. These patients presented the classic symptoms of meningitis less often than other patients, as a previous retrospective study also showed.[7] This may be due to immunosuppression, but also to the fact that this group is older and known for atypical presentations.[7–9,29,32] The lower incidence of peripheral blood leukocytosis may reflect deficits in B- and T-cell immunity due to radiation, intensive chemotherapy, bone marrow infiltration by malignant cells, and corticosteroid therapy.[29] In contrast, the clinical presentation of patients with cancer was similar to that of patients without cancer in a recent study.[11]

Not surprisingly, we found that patients with cancer had more comorbid conditions, aside from cancer itself, and this may have had an impact on the etiology and prognosis of BM.

Our investigation showed that *L. monocytogenes* was the commonest pathogen in patients with cancer, and much more frequent than in patients without cancer, followed by *S. pneumoniae*, with no differences between patients with solid or hematological tumors. *L. monocytogenes* is an infectious agent that is well known for affecting newborns, pregnant women, the immunosuppressed, and the elderly.[5,8,33,34] Classic meningeal pathogens, such as meningococci, are not a significant cause in cancer patients. In a recent study,[11] patients with active cancer were more likely to be infected with

Table 4

Multivariate analysis for effect on unfavorable outcome.

Variable	Odds ratio	95% CI	P
Shock	11.207	5.024–24.997	<.001
Coagulation disorder	4.455	1.665–11.925	.003
Inappropriate initial antibiotic	3.774	1.742–8.176	.001
Age (≥65 years)	2.581	1.490–4.472	.001
Acute renal disorder	2.223	1.176–4.200	.014
Cancer	1.825	0.941–3.539	.075
Positive blood culture	1.577	0.877–2.837	.128
Charlson comorbidity index ≥3	1.491	0.788–2.822	.219
Impaired mental status	1.346	0.719–2.522	.353
Etiology			
Neisseria meningitidis	1.000 (reference)		
Streptococcus pneumoniae	9.421	3.104–28.598	<.001
Listeria monocytogenes	10.254	2.834–37.098	<.001
Gram-negative bacilli	25.668	6.888–95.648	<.001
Other microorganisms	9.685	3.148–29.795	<.001

CI = confidence interval. Nagelkerke R^2 for the adjusted model = 0.473.

L. monocytogenes than patients with inactive cancer or without cancer although overall the most important causative pathogen was *S. pneumoniae*.

Other differences included a higher probability of having received out-of-hospital antibiotic therapy, which could explain the low rate of positive CSF Gram-stained smears and episodes of unknown etiology (25%). On the other hand, the CSF parameters did not differ between the 2 groups, although underlying immune suppression, together with the predominance of listeria as a cause, could lead to changes in CSF cell counts.

Cerebral CT before spinal tap is 1 of the changes in the management of BM introduced in recent years.[4,35] Current international guidelines use papilledema, focal neurological signs, moderate-to-severe impairment of mental status, an immunocompromised state, and new-onset seizures as "red flags" for identifying patients at an increased risk of a cerebral mass lesion and elevated intracranial pressure, for whom cerebral CT is recommended before LP.[24] Following these guidelines, CT was more frequently performed among cancer patients in our study, although this was associated with an increased ATI, which carries a worse prognosis.[3,4,36,37] This interval needs to be reduced; therefore, if we want to improve the outcome for our patients, a high index of suspicion is necessary for acute BM, and assuming that a CT brain scan is performed before LP on most of these patients if the radiological procedure is readily available, antibiotics should not be delayed and should be administered beforehand.[3,11]

Treatment of BM in adults has shifted toward the use of third-generation cephalosporins. But in this group of patients, if the CSF Gram stain is highly suggestive of nonstreptococcal organisms, or negative, empiric antibiotic coverage should always include *L. monocytogenes*[3,5]; in our analysis; however, 32% of the patients did not receive this treatment that is recommended in current guidelines.[38,39]

Compared to patients with meningitis in the general population, we found a higher mortality rate among patients with cancer,[6,9,10,13] with no improvement between the 2 periods and no differences with respect to neurological and systemic complications. Independent factors associated with an unfavorable outcome by multivariate analysis included age 65 or older, shock, coagulation disorder, acute renal failure, inappropriate initial antibiotics, and an etiology different from *N. meningitidis*. The higher mortality among cancer patients may have been the result of inadequate empiric treatment or infection caused by pathogens with a worse prognosis, such as *L. monocytogenes*, rather than cancer itself (which was not associated with increased mortality in the adjusted model).

Patients with malignancies however developed fewer sequelae after the meningitis episode. The number of patients with sequelae in our study is very small (6), so it is difficult to come to a conclusion; it is possible that cancer patients could not survive severe infection, which usually results in neurological sequelae. Nevertheless, we cannot exclude that this difference could come from the different etiology of the meningitis

5. Limitations

Our study is based on a single hospital, which could imply that the results would apply only to places with similar local ecologies and populations to ours. Second, the number of cases was relatively small, although the present study is one of the largest. Third, the long study period may have integrated different issues to do with global epidemiology due to modified medical procedures, modern cancer treatments, antimicrobial resistance, and the introduction of vaccines in the population.

In summary, BM remains a highly lethal complication in cancer patients, despite modern antibiotic therapy. Our study demonstrates that the microbial etiology and manifestations of meningitis in cancer patients differ from those in other patients. The higher mortality among patients with cancer may be the result of the longer time interval from admission to antibiotic therapy and greater frequency of inappropriate empiric antibiotic treatment. A high index of suspicion for meningitis and early initiation of adequate empiric antimicrobial therapy (including treatment of *L. monocytogenes*) could prevent deaths in cancer patients.

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