

BRIEF REPORT

LISTERIA BACTEREMIA IN PATIENTS FROM A PERUVIAN ONCOLOGIC INSTITUTE, 2005-2015

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ABSTRACT

Listeriosis infection is a severe disease, with high morbidity and mortality in the immunocompromised patient, especially with disseminated and fatal presentations in cancer patients. A descriptive study was developed to describe the clinical and epidemiologic characteristics in oncologic patients with listeriosis in the Instituto Nacional de Enfermedades Neoplásicas between the years 2005-2015. A total of 29 patients were included; 23 (79.3%) of the listeriosis cases showed up in patients with hematological neoplasia, of which 52.1% was acute lymphatic leukemia and 39.1% non-Hodgkin's lymphoma. The 72.4% of the isolated species correspond to *Listeria monocytogenes*. Twenty-seven (93.1%) patients met sepsis criteria and twenty-four (82.7%) had neurologic affection. Bacteremia was the most common presentation, followed by meningoencephalitis (20.6%). Global mortality was 75.8%. In conclusion in cancer patients, listeriosis implies high morbidity and mortality. Therefore, the suspicion of this entity is mandatory in onco-hematologic patients with sepsis and acute neurologic symptoms.

Keywords: Listeria; Neoplasms; Bacteremia; Peru (source: MeSH NLM).

INTRODUCTION

Listeria monocytogenes is a gram-positive, facultative anaerobe bacillus responsible for 90% of human infections by the *Listeria* genus⁽¹⁾. Listeriosis manifests in different forms, from self-limited gastroenteritis in immunocompetent patients to bacteremia, meningoencephalitis and rhombencephalitis, due to dissemination and greater severity in immunocompromised patients. In pregnant women it may cause abortion or fetal death^(1,2).

In more than 70% of cases, listeriosis occurs in vulnerable groups such as immunocompromised patients, patients over 60 years of age, neonates, pregnant women, patients with hepatopathy, diabetes and cancer; the latter representing more than 30% of all cases⁽³⁾. In cancer patients, listeriosis is most frequently observed in chronic lymphocytic leukemia (21%), acute lymphocytic leukemia (ALL) (12%) and Hodgkin's lymphoma (12%), with a mortality of up to 32% compared to 27% in other vulnerable patients^(4,5).

In cancer patients, the greater frequency and severity of listeriosis is due to the greater number of risk factors⁽⁵⁾; however, the information available in the medical literature on this subject is still scarce. In this regard, we present a descriptive study about the clinical and epidemiological characteristics of patients with listeriosis seen at the Instituto Nacional de Enfermedades Neoplásicas between 2005 and 2015.

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THE STUDY

Twenty-nine cases of listeriosis were identified through the review of the culture database of the Microbiology Department of the Instituto Nacional de Enfermedades Neoplásicas (INEN) in the period 2005-2015. Patient information regarding epidemiological aspects, comorbidities, neoplasia, clinical manifestations, laboratory and imaging, as well as the antibiotic treatment provided, corticotherapy, chemotherapeutic agents and clinical outcome, was obtained from the medical records.

An elderly patient was considered as a patient 65 years of age or older. The diagnosis of listeriosis was established if the patient had signs or symptoms of infection, associated with a positive blood and/or cerebrospinal fluid (CSF) culture for *Listeria* species. Confirmed case with meningoencephalitis by *Listeria* was defined as a patient with central nervous system (CNS) impairment, either with sensory disturbance, seizures and/or meningeal signs, associated with fever, pleocytosis, with or without bacteremia by *Listeria*, with or without alterations in imaging studies and positive CSF culture. The diagnosis of sepsis due to *Listeria* was established as the presence of systemic inflammatory response syndrome, associated with a positive culture. Neutropenia was defined as a neutrophil count <1000 per mL and lymphopenia as <1000 lymphocytes/mL. In CSF studies, excess of cerebrospinal fluid proteins was defined as >600 mg/L, pleocytosis >5 cells/mL and glucose consumption was defined as CSF glucose/serum glucose ratio <0.4.

Antibiotic sensitivity tests were performed using the disk diffusion technique (Kirby-Bauer), in accordance with international standards of the Clinical and Laboratory Standards Institute (CLSI). The minimum inhibitory concentration (MIC) for some antibiotics was obtained from the results issued by the BD Phoenix automated system, although there are no cut-off points for this microorganism. On some occasions the MIC was issued without reference cut-off points or, failing that, the cut-off points of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were taken into account.

The diagnosis that justified the antibiotic treatment was febrile neutropenia. Empirical therapy consisted of meropenem sometimes associated with vancomycin, to which ampicillin (12 g/day) was added once the result of gram-positive bacilli in blood or CSF was obtained. Response to antibacterial therapy was defined as the resolution of signs or symptoms of infection, including negative cultures or imaging improvement. On the other hand, failure of

KEY MESSAGES

Motivation for the study: In cancer patients, listeriosis has a disseminated behavior with frequently fatal outcomes. Empirical therapy is often delayed due to lack of clinical suspicion.

Main findings: Most (79.3%) of the cases of listeriosis were found in patients with hematologic neoplasms. On admission, twenty-seven (93.1%) patients met criteria for sepsis and twenty-four (82.7%) had some type of neurological impairment: sensorium disorder (79.3%), meningeal signs (51.7%), and seizures (24.1%).

Implications: Listeriosis should be suspected in any oncohematologic patient with sepsis and acute neurologic impairment until cultures are obtained.

antibacterial therapy was defined as clinical deterioration of the patient, including worsening of laboratory and imaging parameters with fatal outcome.

Clinical outcome was assessed by patient follow-up recorded in the medical record up to 60 days after the positive culture for *Listeria*, categorized as response or failure to antibacterial treatment.

We conducted a descriptive analysis using the statistical program Stata 12.0 (Stata Corporation, College Station, Texas, USA), with which we obtained frequencies and percentages for qualitative variables and mean with standard deviation or median with interquartile range (IQR) for quantitative variables.

The research was approved by the Protocol Review Committee of the Research Department of INEN prior to its implementation (INEN N° 16-57). No intervention on human beings was carried out. We maintained the right to confidentiality of the clinical records analyzed.

FINDINGS

Most of the cases (65.5%) registered in the last decade were clustered from 2010 to 2015, with lower percentages during the previous years. A greater distribution was obtained during the summer and autumn months (62%); with lower figures during the winter (17%).

Twenty-nine oncologic patients with listeriosis were identified with a median age of 54 years (RIQ 11-61). Twenty-three cases (79.3%) showed hematologic neoplasms and 20.6% showed solid neoplasms (Table 1). In addition to

the background neoplasm, there were 9 (31%) patients with other comorbidities: arterial hypertension (n=2) and liver cirrhosis, diabetes mellitus, hypothyroidism, schizophrenia, G6PD deficit, HBV infection and HTLV 1-2 infection with one case per disease.

In 18 (62%) patients there was previous use of anti-H2 blockers or proton pump inhibitors (PPI). Twenty-seven (93.1%) were receiving corticosteroids at the time of infection. The chemotherapy regimens are detailed in Table 2.

On admission, twenty-seven (93.1%) met sepsis criteria and twenty-four (82.7%) had some type of neurological impairment [sensory disturbance: 23 (79.3%), meningeal signs: 15 (51.7%) and seizures: 7 (24.1%)]. The most common presentation was bacteremia, observed in all twenty-nine

Table 1. Characteristics of patients with listeriosis at the Instituto Nacional de Enfermedades Neoplásicas, 2005-2015 (n=29).

Characteristics	n (%)
Age (years)	
<18	9 (31.0)
<18-65	14 (48.3)
>65	6 (20.7)
Sex	
Male	17 (58.6)
Female	12 (41.4)
Background neoplasm	
Hematologic neoplasm	23 (79.3)
Solid tumor	6 (20.7)
Hematologic neoplasm	
Acute lymphatic leukemia	12 (52.3)
Acute myeloid leukemia	1 (4.3)
Non-Hodgkin's lymphoma	9 (39.1)
Multiple myeloma	1 (4.3)
Solid tumor	
Lung neoplasm	2 (33.2)
Breast neoplasm	1 (16.7)
Cervical neoplasm	1 (16.7)
Synovial sarcoma	1 (16.7)
Gestational trophoblastic disease	1 (16.7)
Time of hospitalization (days)	
<5	11 (37.9)
5 or more	18 (62.1)
Presentation	
In-hospital	10 (34.5)
Out-of-hospital	19 (65.5)

In-hospital presentation: listeriosis developed during hospitalization.

Out-of-hospital presentation: listeriosis as part of the clinical picture on admission.

Table 2. Chemotherapeutic regimens in patients with listeriosis at the Instituto Nacional de Enfermedades Neoplásicas, 2005-2015 (n=29).

Chemotherapy regimen	n (%)
Vincristine-DNM-L asparaginase	7 (24.1)
CHOP	5 (17.2)
Paclitaxel-Carboplatin	2 (6.9)
Alentuzumab	1 (3.4)
Other	14 (48.3)

DNM: daunorubicin; CHOP: chemotherapy regimen consisting of vincristine, doxorubicin, cyclophosphamide and prednisone.

patients, in six of whom (20.6%) there was also positive CSF culture. The most frequent associated superinfection was bacteremia due to *Pseudomonas aeruginosa* (10.3%).

Isolations of *Listeria* sp. were reported during specific time periods, due to laboratory limitations in identifying the species involved. *Listeria monocytogenes* accounted for 72.4% of the species isolated (Table 3). Ampicillin, vancomycin and meropenem were the most empirically employed antibiotics. *In vitro* sensitivity to ampicillin was identified in 21 (84%) patients (Table 4). Four patients presented neurological sequelae (13.7%), of which 50% had positive CSF culture. Of the 29 patients with bacteremia, 75.8% died (overall mortality); while overall mortality in confirmed meningoencephalitis was 16.6%. It was not possible to calculate mortality attributable to listeriosis.

DISCUSSION

Listeriosis is a public health problem because it is one of the most common foodborne diseases. In the United States, despite having a low incidence in the general population (0.1 to 1 cases per 100,000 inhabitants), it is responsible for 19% of deaths due to ingestion of contaminated food of known etiology, a figure similar to that of France, where it represents 17% of the total ^(6,7). A cross-sectional study carried out in the city of Ica (Peru), collected 74 samples of fresh cow's milk cheese of artisanal production, from the main markets supplying the local public. Twenty-eight isolates (20.7%) of the total sample were found to be contaminated by colonies suggestive of *Listeria*; cow's milk was the probable source of contamination during processing ⁽⁸⁾.

The results of our study show a greater concentration of cases in the last five years, with a higher frequency during the summer and autumn months, which is in concordance with other reports, where the summer months, especially in countries of the northern hemisphere, show a greater

Table 3. Laboratory, imaging and microbiological characteristics of patients with listeriosis at the Instituto Nacional de Enfermedades Neoplásicas, 2005-2015 (n=29).

Characteristics	n (%)
Leucocytes (cells/mL)	
< 4,000	14 (48.3)
4,000-12,000	11 (37.9)
> 12,000	4 (13.8)
Neutrophils (cells/mL)	
< 100	8 (27.6)
100-500	0
500-1,000	1 (3.4)
> 1,000	20 (69.0)
Lymphocytes (cells/mL)	
< 1,000	27 (93.1)
CSF	
Proteins > 600 mg/L	17 (85.0)
> 5 cells	16 (80.0)
CSF glucose/serum glucose Id < 0.4	9 (45.0)
Brain CT	
Brain abscess/cerebritis	2 (9.5)
Indirect signs of meningitis	1 (4.8)
Secondary infiltration	4 (19.0)
Other	6 (28.6)
No significant alterations	8 (38.1)
Microbiological species	
<i>Listeria monocytogenes</i>	21 (72.4)
<i>Listeria ivanovii</i>	1 (3.4)
<i>Listeria sp.</i>	7 (24.1)

CSF: cerebrospinal fluid; CT: computed axial tomography; Id: index.

number of cases^(9,10). Cairns *et al.* mathematically associated the increase in the number of cases with the increase in climatic temperature⁽¹⁰⁾. However, the results described differ from those of Sedano *et al.*, who reported in Chile that 10% of cases occur in the summer months, arguing that this is because of the higher consumption of contaminated frozen vegetables in the remaining months, which would act as a means of transmission⁽¹¹⁾.

Listeriosis in oncologic patients occurs frequently in those with hematologic neoplasms, and a greater number of cases were observed in cases of acute lymphatic leukemia and non-Hodgkin's lymphoma (NHL), both lymphoreticular neoplasms. The control of the infection by *Listeria monocytogenes* requires cellular immunity as it is an intracellular agent, requiring an adequate T helper 1 response, with concomitant participation of macrophages from the innate immune system^(12,13). ALL and NHL,

Table 4. Antibiotic sensitivity profile.

Antibiotic sensitivity	n (%)
Ampicillin	21 (84)
Gentamicin	24 (85.7)
Cotrimoxazole	17 (77.2)
Penicillin	3 (75.0)
Meropenem	27 (100)
Vancomycin	25 (96.1)

which represent more than 70% of cases in this series, are characterized by being neoplasms that alter cellular immunity, predisposing to severe and disseminated disease. Aggravating factors include advanced age, corticotherapy and lymphopenia, observed in 20%, 93% and 93% of cases, respectively.

Since this is an infection which enters through the gastrointestinal tract, one of the first lines of defense is the acidity of the gastric juice; it has been previously described that the consumption of medications that modify the gastric pH (alkalinizing it) could be risk factors for the development and progression of the disease⁽¹⁴⁾. The use of PPIs or H2 antagonists in this series was 62% of the total cases, which could have acted as an additional risk factor.

In accordance with the literature, bacteremia as sepsis was the most frequent manifestation (93.1%), followed by confirmed meningoencephalitis (20.6%)⁽¹²⁻¹⁴⁾. However, we observed that 82.7% of patients presented some type of acute neurological involvement at admission, suggesting that there may be underdiagnosis of meningoencephalitis due to *Listeria sp.*

In this case series, 34.5% of cases occurred during hospitalization, a rather high figure when contrasted with other series that range from 8.7% to 30% of cases⁽¹⁵⁾. Nosocomial outbreaks have been associated with the consumption of contaminated food, so it is important to reinforce strict quality control in the administration of food in health care institutions for oncohematologic patients. Another hypothesis suggests the asymptomatic carrier state, the prevalence reported to be 10%, with subsequent clinical expression of disease after immunosuppressive therapy⁽¹⁶⁾.

The isolation of *Listeria ivanovii* in blood culture, which has been described as a pathogen only in ruminants, is of interest. There are extremely rare reports of disease in severely immunocompromised humans. Gastroenteritis and bacteremia are described, being considered as a possible opportunistic enteric human enteric pathogen⁽¹⁷⁾.

Diagnosis and treatment of listeriosis should be timely and early. Meropenem with/without vancomycin was the most commonly used empirical therapy, since febrile neutropenia was the initial diagnosis. Later, ampicillin was added when large positive bacilli were reported in blood or CSF samples. Ampicillin associated with gentamicin is the most recommended combination for immunocompromised patients^(18,19). There is no official consensus on the duration of treatment; however, recommendations suggest a minimum of three weeks. Experts recommend individualizing therapy: bacteremia (2 weeks), meningitis (3 weeks), endocarditis (4 to 6 weeks) and encephalitis or brain abscess (5 to 8 weeks)⁽¹⁸⁻²⁰⁾.

This study has the limitations inherent to any retrospective study, as its results are based on clinical records. Therefore, it was not possible to accurately obtain the mortality attributable to listeriosis. In addition, due to temporal technical limitations

in the microbiology department, we were unable to identify the listeria species in all the isolates.

In conclusion, this study shows that listeriosis has an aggressive and disseminated behavior in oncological patients, leading to high morbimortality, so this diagnosis should be suspected preferably in all patients with hematological neoplasms who present sepsis and acute neurological impairment.

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