

# SEPSIS DUE TO *LISTERIA MONOCYTOGENES* IN AN IMMUNOCOMPROMISED PATIENT WITH PERITONEAL CARCINOMATOSIS: A CASE REPORT

BAĞIŞIKLIĞI BASKILANMIŞ, PERİTONEAL KARSİNOMATOZİSLİ BİR HASTADA *LISTERIA MONOCYTOGENES*'E BAĞLI SEPSİS: OLGU SUNUMU

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## ABSTRACT

*Listeria monocytogenes* is an opportunistic infectious agent that can cause self-limiting gastroenteritis in immunocompetent individuals, usually with the consumption of contaminated foods, and fatal infections in immunocompromised individuals and newborns. Local effects of intra-abdominal tumors, immune response suppression, and operations that disrupt the integrity of the peritoneal membrane and gastrointestinal tract may increase the risk of pathogen-induced invasive infection. Although cytoreductive surgical interventions, systemic and/or hyperthermic intraperitoneal chemotherapy (HIPEC) applied in the treatment of patients with abdominal and pelvic malignancies increase disease-free survival, they may predispose to infections caused by *L. monocytogenes* through gastrointestinal and systemic complications. In this case report, a 71-year-old male patient diagnosed with sepsis due to *L. monocytogenes* after treatments with systemic chemotherapy and cytoreductive surgery combined with HIPEC is discussed. It is aimed to raise clinical and laboratory awareness that *L. monocytogenes* may cause systemic and life-threatening infections in individuals whose immune system is suppressed due to cancer, surgical procedures, and the use of chemotherapeutic agents.

**Keywords:** Hyperthermic intraperitoneal chemotherapy, *Listeria monocytogenes*, peritoneal carcinomatosis, systemic chemotherapy, sepsis

## ÖZET

*Listeria monocytogenes*, immünokompetan bireylerde genellikle kontamine olmuş gıdaların tüketilmesi ile kendi kendini sınırlayan gastroenterit tablosuna, immun sistemi baskılanmış bireylerde ve yenidoğanda ise ölümcül enfeksiyonlara yol açabilen fırsatçı bir enfeksiyöz ajandır. Karın içi tümörlerin lokal etkileri, immün yanıtın baskılanması, peritoneal membran ve gastrointestinal sistemin bütünlüğünü bozan operasyonlar patojen kaynaklı invaziv enfeksiyon riskinde artışa neden olabilir. Abdominal ve pelvik maligniteleri olan hastaların tedavisinde uygulanan sitoreduktif cerrahi girişimler, sistemik ve/veya hipertermik intraperitoneal kemoterapi (HIPEK) hastalıksız sağkalımı arttırmakla birlikte gastrointestinal ve sistemik komplikasyonlar yoluyla *L. monocytogenes*'in neden olduğu enfeksiyonlara zemin hazırlayabilir. Bu olgu sunumunda, sistemik kemoterapi ve sitoreduktif cerrahi ile kombine HIPEK tedavileri sonrası *L. monocytogenes*'e bağlı sepsis tanısı alan 71 yaşında bir erkek hasta tartışılmış ve *L. monocytogenes*'in kanser, cerrahi işlem ve kemoterapötik ajanların kullanımı gibi sebeplerle immün sistemi baskılanmış bireylerde sistemik ve hayatı tehdit edici enfeksiyonlara neden olabileceği konusunda klinik ve laboratuvar farkındalığı yaratmak amaçlanmıştır.

**Anahtar Kelimeler:** Hipertermik intraperitoneal kemoterapi, *Listeria monocytogenes*, peritoneal karsinomatozis, sistemik kemoterapi, sepsis

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## INTRODUCTION

*Listeria monocytogenes* is a Gram-positive, catalase-positive, oxidase-negative, indole-positive, motile, and non-spore-forming intracellular rod that causes foodborne outbreaks worldwide (1). It can be found in many foods such as vegetables, fruits, seafood, meat, and dairy products and is one of the leading causes of food-related mortality (2). It is the cause of foodborne gastroenteritis in immunocompetent individuals; sepsis, and meningitis in newborns; postpartum infections, meningoencephalitis, bacteremia, and sepsis in immunocompromised individuals (3). Cases of cutaneous listeriosis, bacterial endocarditis, hepatitis, liver abscess, peritonitis, biliary tract infections, and musculoskeletal infections have also been reported (4). According to somatic and flagellar antigen-based serotyping methods, four main serotypes defined as 1/2a, 1/2b, 1/2c, and 4b are responsible for most clinical cases, while serotype 4b is responsible for food-related outbreaks and sporadic diseases (5). Sporadic cases may be seen more frequently in the spring and summer with increased consumption of high-risk food products (4). Antimicrobial therapy is the only treatment option for listeriosis and the ampicillin plus gentamicin combination is the most used treatment choice. Trimethoprim/sulfamethoxazole combination can also be used as an alternative antibiotic (6). Although it is less common than other foodborne infections, listeriosis is an important public health problem in immunocompromised individuals due to its mortality rate of 30% despite appropriate antibiotic therapy (7,8). Although hyperthermic intraperitoneal chemotherapy used in peritoneal malignancies has less toxicity than systemic administration, attention should be paid to its local effects such as inflammatory reactions in the peritoneum, intraabdominal infections, bowel obstruction, and delayed wound healing (8). We present a case report of sepsis due to *L. monocytogenes* in a 71-year-old male patient who received systemic chemotherapy and cytoreductive intra-abdominal surgery combined with HIPEC for peritoneal carcinomatosis.

## CASE REPORT

A 71-year-old male patient was followed up with the diagnosis of peritoneal carcinomatosis secondary to prostate cancer applied to the emergency service of Gülhane Training and Research Hospital on 03.06.2022 with complaints of weakness, inability to walk, and confusion. In his past medical history, he had a transurethral prostatectomy in 2019 and received a total of 14 cycles of chemotherapy, and in February 2022, cytoreductive surgery (CRS) and HIPEC were applied. At the time of admission, the general condition of the patient was moderate, and he was unconscious. The Glasgow coma scale score of the patient was calculated as 10. Spontaneous movements in the bilateral lower and upper extremities were

observed and in ophthalmological examination pupils were normoisochoic. The patient had a fever of 38°C with no history of antibiotic use. The patient's laboratory findings were detected as follows: WBC:  $1.6 \times 10^3$  cell/mm<sup>3</sup> ( $3.9 \times 10^3$ - $10.9 \times 10^3$ ), neutrophil ratio: 91% (41-70.7), lymphocyte ratio: 2.2% (19.1-47.9), thrombocyte:  $3 \times 10^3$  cell/mm<sup>3</sup> ( $173 \times 10^3$ - $360 \times 10^3$ ), Hb: 7.4 g/dL (13.5-16.9), Hct: 21.6 % (40-49.4), urea: 137 mg/dL (17-43), creatinine: 2.67 mg/dL (0.84-1.25), CRP: 151.7 mg/L (0-5), procalcitonin: 14.3 ng/mL (0-0.65), sedimentation rate: 118 mm/h (0-20), prothrombin time: 26.3 sec (9.7-14.3), INR: 2.32 (0.8-1.2). Pancytopenia was observed according to the results of the complete blood count and peripheral smear. He was admitted to the neurosurgery intensive care unit with clinical suspicion of disseminated intravascular coagulation (DIC) and sepsis.

Blood cultures taken from the patient were inoculated into a pair of aerobic and anaerobic blood culture bottles and incubated for five days in a blood culture instrument (Zhuhai Medical Technology, China). Both aerobic and anaerobic blood cultures gave positive signals after 24 hours and were subcultured on 5% sheep blood, eosin methylene blue (EMB), and chocolate agar.  $\beta$ -hemolytic colonies were observed on blood agar after 24 hours of incubation at 37°C with 5% CO<sub>2</sub>. In Gram staining, Gram-positive rod morphology was observed. The bacterium was catalase positive, oxidase negative, and indole positive in the biochemical tests. The isolate was identified as *L. monocytogenes* using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Germany). Antibiotic susceptibility testing was determined by the disc diffusion method according to European Committee on Antimicrobial Susceptibility Testing criteria (9). The isolate was detected as susceptible to benzylpenicillin, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, and meropenem. Ampicillin (2 g IV every 4 hours) and meropenem (1 g every 12 hours) were started as treatment. Despite all treatments, the patient was deceased on 12.06.2022. Informed consent was obtained from the patient.

## DISCUSSION

*Listeria monocytogenes* are commonly found in natural environments such as soil, surface water and groundwater, sewage, and animal feeds. It has been isolated from ruminant farm animals' meat, dairy, and poultry products and from flies and ticks. *L. monocytogenes* is considered a rare but serious intracellular infectious agent, especially for neonates, elders, and immunocompromised individuals. Listeriosis is mainly occurred in humans by digesting contaminated food (10,11). Gastrointestinal adaptation is required for entrance to the host. The virulence gene that plays an important role in this adaptation is *sigma B* (10).

The pathogen has glutamate decarboxylase (GAD), arginine deaminase (ADI), and agmatine deiminase (AgDI) systems against low pH in the gastrointestinal tract (12). Tolerance to bile salts is achieved by increasing the expression of the multi-drug efflux pump so that it can colonize the liver and gallbladder (10). After colonization, it can cross the intestinal barrier in three different ways: directly, through invasion into enterocytes, or through Peyer's patches (13). Internalization occurs by binding to the extracellular domain of E-cadherin molecule in epithelial cells with the surface proteins InlB, InlC, and InlJ belonging to the internalin family (13). The listeriolysin O (LLO) toxin allows the pathogen to escape from the phagosomes. Cell-to-cell spread is achieved by actin polymerization (13,14).

Bacterial translocation is thought to be the main mechanism responsible for *L. monocytogenes* sepsis. Invasion of enteral bacteria from the epithelial mucosa of the gastrointestinal tract to the lamina propria, mesenteric lymph nodes, and other possible organs, respectively is called a bacterial translocation (15). It is known that changes in the enterobacterial flora, damaged intestinal barrier, and decreased host immunity cause bacterial translocation (15,16). Any chemotherapeutic or radiotherapeutic administration that causes loss of gastrointestinal mucosal integrity and reduces liver, spleen, and peritoneal macrophage functions may increase the risk of invasive infections (4).

Systemic chemotherapy, intra-abdominal cytoreductive surgery combined with HIPEC, damage to the peritoneal mesothelial cells, and local effects of the tumors were thought to be risk factors in the patient with *L. monocytogenes* sepsis. It is known that topical and high-concentration application of heated chemotherapeutics to the peritoneum to target microscopic tumor fragments after cytoreductive surgery may increase recovery rates in cancer patients while causing complications such as fistula, abscess, anastomotic leakage, perforation, and post-operative sepsis (17). Studies show that HIPEC administration increases the risk of infection by 43% (17). In the presented study, the risk factors mentioned above may cause mesothelial cell and gastrointestinal mucosal barrier injury, decreased intestinal motility, and impairments in local and systemic immune responses. All of these may prepare the ground for translocation and invasive infection of *L. monocytogenes*. Implementing infection control procedures and taking precautions against bacterial translocation are essential steps to prevent invasive intestinal infections in immunosuppressive patients.

According to the European Food Safety Authority (EFSA), data, 2,183 invasive *L. monocytogenes* cases (923 hospitalizations, 196 deaths) were detected in Europe in 2021. The most common cause of the exposure was reported

as foodborne transmission. Samples taken from different food categories revealed that most of the foods contaminated with *L. monocytogenes* are refrigerated ready-to-eat (RTE) and meat products (3.1%) (18). In a study including fresh meat samples sold in supermarkets, butchers, and retail shops in Türkiye, the contamination rate of meats with the bacterium was found to be 12.8% (19). Ensuring food hygiene in the manufacturing or distribution stages is one of the most important steps to be taken to prevent listeriosis cases.

In Doganay's study, which included 32 cases of *L. monocytogenes* reported in Türkiye between 1987 and 2001, it was reported that the pathogen most frequently (21-43%) caused sepsis progressing to DIC in immunocompromised hosts (20). Aktaş et al. reported a case of sepsis due to *L. monocytogenes* in a 49-year-old patient diagnosed with febrile neutropenia and pleomorphic carcinoma. They observed that the infection was successfully treated after the initiation of piperacillin/tazobactam and amikacin (21). Ağuş et al. reported a case of sepsis due to *L. monocytogenes* in a 61-year-old patient who received systemic chemotherapeutics for chronic lymphocytic leukemia. Ampicillin/sulbactam and imipenem were started but the patient was deceased on the second day of hospitalization (22). Yıldız et al. conducted a retrospective study including 9 cases of listeriosis reported in Türkiye between 1991 and 2002. The remarkable feature of this study is that all patients who developed sepsis (5/9) had an underlying malignancy and a history of immunosuppressive therapy. These patients received different treatment combinations from each other, such as oral ampicillin/sulbactam, imipenem alone, and amikacin combined with penicillin or imipenem. However, the results of the study showed that different antibiotic regimens did not affect the mortality rate (23). In treatment, penicillin G or ampicillin is used as the first choice. Aminoglycosides combined with ampicillin are known to have synergistic effects. Meropenem and trimethoprim/sulfamethoxazole can be used as alternative treatment options. Multidrug-resistant *L. monocytogenes* isolates have also been reported (6,22,23). It should be kept in mind that there is high mortality despite appropriate antibiotic treatment and the risk of progression to sepsis is higher in immunocompromised patients.

In conclusion, we encountered a case of sepsis due to *L. monocytogenes* in an immunocompromised patient who received systemic chemotherapy and cytoreductive surgery combined with HIPEC for the treatment of peritoneal carcinomatosis. Serious precautions against invasive infectious agents should be taken in immunosuppressive patients receiving systemic and local chemotherapy. In addition, we conclude that awareness among clinicians and laboratories should be raised in *L. monocytogenes* which has an increasing incidence and causes fatal out-

comes in immunosuppressive patients to help advances in treatment and reduce mortality rates.

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