

# *Listeria Monocytogenes* Meningitis After Allogeneic Bone Marrow Transplantation in a Patient with Myelodysplastic Syndrome-Refractory Anemia with Excess Blasts: Case Report

## Miyelodisplastik Sendrom-Aşırı Blastlı Refrakter Anemi Tanılı Hastada Allogeneik Kök Hücre Nakli Sonrası Görülen *Listeria Monocytogenes* Menenjitisi

Erhan ALKAN, MD,<sup>a</sup>  
Ayşen TİMURAĞAOĞLU, MD,<sup>b</sup>  
Rabin SABA, MD<sup>c</sup>  
Dilara Meral ÖĞÜNÇ, MD<sup>d</sup>

Departments of  
<sup>a</sup>Internal Medicine,  
<sup>b</sup>Hematology,  
<sup>c</sup>Clinical Infections Disease,  
<sup>d</sup>Microbiology,  
Akdeniz University Faculty of Medicine,  
Antalya

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Yazışma Adresi/Correspondence:  
Ayşen TİMURAĞAOĞLU, MD  
Akdeniz University Faculty of Medicine,  
Department of Hematology, Antalya,  
TÜRKİYE/TURKEY  
aysentimuragaoglu@yahoo.com

**ABSTRACT** Viral, fungal and bacterial infections are commonly seen in patients early after the allogeneic bone marrow transplantation (BMT), because of neutropenia in the early period, later they occur due to cell mediated immune deficiency and at the late post transplant period due to immunoglobulin deficiency. *Listeria monocytogenes* is a gram positive bacterium that invades and proliferates in macrophages and epithelium. Because it is an intracellular bacterium, besides its virulence, host immune system is also important for defence mechanism against bacterium. Life threatening bacteriemia and meningitis caused by *L. monocytogenes* are generally seen in newborns, elderly and immunosuppressive patients including organ recipients. Herein we reported a patient who had allogeneic BMT due to myelodysplastic syndrome-refractory anemia with excess blasts (MDS-RAEB), presented with *L. monocytogenes* meningitis six months after allogeneic transplantation.

**Key Words:** Bone marrow transplantation; immunosuppression; meningitis, listeria

**ÖZET** Allogeneik kök hücre nakli sonrası akut dönemde nötropeni, daha sonra hücre sel immun yetmezlik ve son dönemde de hipogamaglobulinemi nedeniyle viral, fungal ve bakteriyel enfeksiyonlara sık rastlanmaktadır. *Listeria monocytogenes* makrofaj ve epitel hücrelerine yerleşen gram pozitif bir bakteridir. Hücre içinde çoğalması nedeniyle konak savunmasında bakterinin virülansının yanısıra konağın bağışıklık sistemi de önemlidir. Hayatı tehdit edici *L. monocytogenes* enfeksiyonlarına ve menenjite özellikle yeni doğan, yaşlılar ve organ nakli yapılmış hastalar da dahil olmak üzere immün sistemi baskılanmış kişilerde sık rastlanmaktadır. Burada, nadir görülmesi nedeniyle, miyelodisplastik sendrom-aşırı blastlı refrakter anemi (MDS-RAEB) tanısı ile allogeneik kemik iliği nakli yapıldıktan altı ay sonra menenjit tablosu ile başvuran ve etken olarak *L. monocytogenes* gösterilen bir olgu sunduk.

**Anahtar Kelimeler:** Kemik iliği nakli; immünsupresyon; listeria menenjitisi

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*Listeria monocytogenes* is a gram positive aerobic bacterium invading macrophages and epithelium and it enters the body via gut following ingestion of contaminated foods. Besides the virulence of the bacteria, cellular immunity is also important for defense against this microorganism. It usually causes a mild gastroenteritis but rarely meningitis in healthy people.<sup>1</sup> Life threatening bacteriemia and meningitis caused by *L. monocytogenes* are generally seen in newborns, geriatric population and immunosuppressive patients including organ recipients.<sup>2,3</sup> We presented a patient with meningitis due to *L. monocytogenes* after allogeneic BMT, a rarely reported case in the literature.

## CASE REPORT

A 49 year-old woman was admitted to our hospital with fever, headache, nausea, vomiting and unconsciousness. She had a history of myeloablative allogeneic BMT due to myelodysplastic syndrome-refractory anemia with excess blasts (MDS-RAEB) six months before. She had been receiving daily 200 mg cyclosporine, 64 mg methylprednisolone, 750 mg ursodeoxycolic acid for hepatic graft versus host disease (GVHD), and prophylactic acyclovir. Physical examination was normal except jaundice, deterioration in neurologic status (poor orientation, neck stiffness), and high temperature (39°C). Laboratory examinations disclosed white blood cells  $5.7 \times 10^9/L$  (80% neutrophils, 15% lymphocytes), platelets  $29 \times 10^9/L$ , hemoglobin 12.6 g/dl, erythrocyte sedimentation rate 52 mm/h, and C-reactive protein 22.9 mg/dl. Her hepatic enzymes, (ALT 142 U/L, AST 45 U/L, GGT 571 U/L, alkaline phosphatase 274 U/L), total and direct bilirubines were high but serum Ig G was slightly low (605 mg/dl). Cerebral MRI was reported as normal. In cerebrospinal fluid (CSF) examination, the pressure was increased, color was xanthochromic, glucose 9.84 mg/dl, protein 32.1 mg/dl, chloride 76 mEq/l, leukocyte  $400/mm^3$  (65% neutrophils, 30% lymphocytes). These clinical and laboratory findings led to the diagnosis of purulent meningitis, and meropenem and vancomycin were administered. Immunosuppressive drugs were stopped. In order to clarify the cause of thrombocytopenia, bone marrow smear was performed which revealed increased percentage of myeloblasts (<20%). Chimerism analysis was done by FISH using sex chromosome probes (her stem cell donor was male) and 50 % donor chimerism was found. Bone marrow examination indicated that the cause of thrombocytopenia was the relapse of MDS. Urine and blood cultures revealed *Escherichia coli* but, cerebrospinal fluid (CSF) culture disclosed *L. monocytogenes*. Both agents were susceptible to meropenem, and vancomycin was changed to amikacin. Although urine and blood cultures were sterile and fever decreased gradually, the patient was still unconscious. Two weeks later, control lumbar puncture was performed but no changes were ob-

served in CSF findings. A treatment consisting of ampicillin and trimethoprim-sulphometoxazol was administered instead of meropenem and amikacin but intravenous immunoglobulins could not be given. During the follow up, the patient's general and neurological status got worse and four weeks later she died due to meningitis in spite of antibiotics and supportive measures.

Since the patient was unconscious, informed consent was obtained from her relatives (husband and daughters).

## DISCUSSION

Viral, fungal and bacterial infections are commonly seen in patients after the allogeneic BMT because of neutropenia in the early period, later they occur due to cell-mediated immune deficiency and at the late post transplant period due to immunoglobulin deficiency.<sup>4</sup> Our patient had allogeneic BMT for MDS-RAEB and was receiving cyclosporine, methylprednisolone and ursodeoxycolic acid for chronic GVHD, and at the same time she had a relapse. Each factor had an effect on the impairment of immune system and contributed to meningitis, however suppression of T cell mediated immunity was probably the most important factor. Cyclosporine administration can be the main cause of disruption of T cell immunity, however it has been known that patients who take glucocorticosteroids also have an increased risk for *L. monocytogenes* infection. During the late phase of allogeneic BMT (>100 days) Varicella zoster, *S. pneumonia*, *H. influenzae* and *N. meningitis* infections are common and the mortality rate of these infections were reported between 4-15%.<sup>5</sup> Chronic GVHD is also one of the contributing factors in these infections by delaying the immune recovery. The mortality rate of *L. monocytogenes* meningitis in patients who did not have BMT was reported as 15-38%.<sup>6</sup> Probably the same immune suppressor mechanisms contribute to *E. coli* sepsis however, although urine and blood cultures got sterile after antibiotherapy, *L. monocytogenes* meningitis did not respond to antibiotherapy or cessation of immunosuppression in our case. Long et al. reported three adult patients with meningitis due to *L. monocytogenes* occurring

4, 7 and 90 months after the BMT. The first patient had undergone allogeneic BMT for MDS and the other two patients for AML. *L. monocytogenes* was cultured from CSF of all patients and all of them recovered with antibiotic therapy.<sup>7</sup> Besides development of *L. monocytogenes* meningitis, septicemia was reported by Want et al. in a six-year-old child with severe aplastic anemia following an unrelated BMT.<sup>8</sup> Zomas et al. reported a *L. monocytogenes* meningitis after allogeneic BMT for CLL that required prolonged maintenance antimicrobial therapy with oral trimethoprim-sulfamethoxazole and intrathecal gentamicin until death of the patient due to chronic GVHD.<sup>9</sup> Rivero et al. reported the lar-

gest group consisting of 11 patients with *L. monocytogenes* infection after BMT.<sup>10</sup> The most common and shared findings in these case reports were chronic GVHD and corticosteroid use which were comparable to our case but these reported cases survived after the antibiotherapy unlike our case.

This is the first case of meningitis reported due to *L. monocytogenes* after allogeneic BMT in our country.

Although it is rare, especially in patients with allogeneic BMT at chronic phase, clinical findings of meningitis must remind *L. monocytogenes* infection in order to guide early diagnosis and treatment.

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