Leuconostoc sp. Meningitis in a Patient Treated with Rituximab for Mantle Cell Lymphoma

Abstract:

We present a 64-year-old man who was treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemoimmunotherapy for mantle cell lymphoma and developed purulent meningitis, probably caused by *Leuconostoc* sp. The patient had severe hypogammaglobulinemia, which is a possible complication of rituximab therapy. To our knowledge and after reviewing the available medical literature, this is the first described case of purulent meningitis caused by *Leuconostoc* sp. in a patient with mantle cell lymphoma that appeared after treatment with the R-CHOP protocol. The diagnosis of purulent meningitis was based on clinical, laboratory and cytological cerebrospinal fluid findings, in addition to blood culture results in which we isolated *Leuconostoc* sp. The patient was treated with meropenem with full recovery.

Key Words: Rituximab, *Leuconostoc*, Purulent meningitis, Mantle cell lymphoma, R-CHOP

Leuconostoc sp. Meningitis in a Patient Treated with Rituximab for Mantle Cell Lymphoma

Mantle Hücreli Lenfoma Tanısı ile Rituksimab Kullanan Bir Hastada Leuconostoc Menenjiti

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Özet: Mantle hücreli lenfoma tanısı ile R-CHOP (rituksimab, siklofosfamid, doksrubisin, vinkristin, prednizolon) kemoimmünoterapi ile tedavi edilen ve muhtemelen *Leuconostoc* cinsi etkene bağlı pürülan menenjit gelişen 64 yaşında bir erkek hastayı sunuyoruz. Hastanın rituksimab tedavisinin olası komplikasyonlarından biri olan ağır hipogammaglobulinemisi bulunmakta olup, bildiğimiz kadardı ile ve mevcut tibbi literatürün taraması sonrasında, olgunuz R-CHOP protokolü ile tedavi sonrası *Leuconostoc* cinsi etkene bağlı pürülan menenjit gelişen mantle hücreli lenfoma tanısı İlk hastadır. Pürülan menenjit tanısı klinik bulgular, laboratuvar ve beyin-omurilik sıvısının sitolojik bulguları ve *Leuconostoc* izole ettiği kan kültürünü temel alıyordu. Hasta meropenem tedavisi ile tamamen iyileşti.

Anahtar Sözcükler: Rituksimab, *Leuconostoc*, Pürülan menenjit, Mantle hücreli lenfoma, R-CHOP

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**Introduction**

Rituximab is a chimeric monoclonal antibody that binds to the CD20 cell surface marker on B lymphocytes. It was approved in the United States in 1997 by the Food and Drug Administration and now is used in 3 major fields: hematological oncology, prevention of transplant rejection, and some autoimmune diseases [1]. After 15 years of global use, due to expansion of its indications and duration of therapy, we begin to see side effects of rituximab therapy that were not previously known [1].

The genus *Leuconostoc* comprises microorganisms previously classified as Lancefield group N streptococci. They are facultative anaerobic, catalase-negative, gram-positive, vancomycin-resistant organisms of cocci form [2]. In nature they are often found on the surfaces of plants, vegetables, and dairy products. They are important bacteria in today’s industry, especially in food fermentation [3]. *Leuconostoc* sp. mainly cause opportunistic infections in immunocompromised patients [3].

**Case Presentation**

A 64-year-old man was admitted to our hospital in March 2011 with generalized lymphadenopathy and hepatosplenomegaly. Based on the clinical and histopathological findings of a resected neck lymph node and epipharyngeal tumor, we diagnosed mantle cell lymphoma stage IV B. The patient was treated with the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) protocol and received 6 cycles of chemoimmunotherapy in 3-week intervals with very good response. He achieved complete remission.

Serum protein electrophoresis performed at diagnosis on 25 March 2011 revealed the following: albumin: 35.58 g/L, alpha 1: 2.94 g/L, alpha 2: 6.3 g/L, beta: 7.74 g/L, gamma: 7.44 g/L. Forty days after the last application of chemoimmunotherapy, on 23 September 2011, he was admitted to the department of infectious diseases of our hospital. At admission he was in a poor condition with severe headache, fever of up to 38.8 °C, and double vision. Upon clinical examination we found that he was conscious and dehydrated, with neck stiffness. Based on these clinical findings, cerebrospinal fluid findings (cells: 3408/3x10⁶/L, erythrocytes: 796x10⁹/L, glucose: 0.9 mmol/L, Cl: 99 mmol/L, protein: 1.04 g/L, 0.87 Sayk neutrophil granulocytes, lymphocytes: 0.10, monocyte-macrophageal cells: 0.03), and the blood culture findings in which *Leuconostoc* sp. was isolated, he was diagnosed to have purulent meningitis. Parameningeal focus such as sinusitis, mastoiditis, otitis media, brain abscess, or spinal epidural abscess was ruled out. The patient lived in the countryside with constant contact with dairy products and other potential *Leuconostoc* habitats, so he had the opportunity to be infected with *Leuconostoc*. In the blood sample results at admission there were 10.1x10⁹/L leukocytes with 83% neutrophils, the C-reactive protein level was 131 mg/L, and the lactate dehydrogenase level was 117 U/L. Electrophoresis of serum proteins showed severe hypogammaglobulinemia (30/09/2011: albumin: 34.95 g/L, alpha 1: 1.15 g/L, alpha 2: 2.1 g/L, beta: 8.4 g/L, gamma: 3.4 g/L). Sensitivity of the isolated pathogen as tested by the Kirby-Bauer method of disk diffusion and the minimum inhibitory concentration (MIC) value for each antibiotic was determined by the E-test method. The pathogen was sensitive to all beta-lactam antibiotics (penicillin MIC of 0.064 mg/L, imipenem (MIC of 0.50 mg/L), macrolides, lincosamides (clindamycin MIC of 0.125 mg/L), and quinolones but was resistant to vancomycin (MIC >256 mg/L). The patient was initially treated with ceftriaxone (2x2 g intravenous), then with ampicillin (6x2 g intravenous) and gentamicin (1x240 mg intravenous), and finally with meropenem (3x2 g intravenous), according to the blood culture findings. With that therapy, his general condition improved with normalization of laboratory parameters of inflammation and he no longer had fever. Control electrophoresis of serum proteins performed before discharge showed an increase in gamma-globulin levels (serum protein electrophoresis, 14/10/2011: albumin: 46.53 g/L, alpha 1: 0.96 g/L, alpha 2: 3.84 g/L, beta: 7.04 g/L, gamma: 5.63 g/L). At the time when patient was treated our biochemistry laboratory could not performed fractions of gamma globulins, so we just have total value. The patient was discharged in good condition with full recovery.

**Discussion and Review of the Literature**

To our knowledge and after reviewing the available medical literature, we conclude that this is the first described case of purulent meningitis that was probably caused by *Leuconostoc* sp. in a patient with mantle cell lymphoma. Meningitis appeared after treatment with the R-CHOP protocol. For certain diagnosis of purulent meningitis caused by *Leuconostoc*, we lack cerebrospinal fluid culture with isolated *Leuconostoc*. Antibiotics having been administered before the lumbar puncture could be the reason why the cerebrospinal fluid culture was negative. The factors in favor for infection with *Leuconostoc* were isolation of *Leuconostoc* from blood culture, the patient being immunocompromised, and good and quick response to the prescribed antibiotic therapy with full recovery. In the literature, most descriptions of infections with *Leuconostoc* are in neonatal and other pediatric patients [4,5,6,7,8,9]. Infections with *Leuconostoc* in adults are rare. *Leuconostoc* can cause endocarditis, urinary tract infections, meningitis, intraabdominal infections, bacteremia, and septicemia.
Central venous catheters and total parenteral nutrition are risk factors for infections with *Leuconostoc*, while newer findings showed that previous antibiotic treatment with vancomycin is not a risk factor for *Leuconostoc* infections [3,7,10]. In most cases, *Leuconostoc* showed good sensitivity to carbapenems (imipenem, meropenem), gentamicin, tobramycin, chloramphenicol, and the more recent daptomycin [3]. However, there is also a report of *Leuconostoc* resistance to carbapenem antibiotics [11].

In the literature, bacterial or viral infections associated with the use of rituximab were described in patients who were receiving maintenance therapy [1,12,13]. In randomized trials in which rituximab was not administered as maintenance therapy, there was no increase in the incidence of infections in patients who were treated with the addition of rituximab to chemotherapy as compared to chemotherapy alone [1,14]. The most common infections described in the literature are reactivation of hepatitis B virus, progressive multifocal leukoencephalopathy caused with JC polyomavirus, enterovirus encephalitis, parvovirus B19 infection, *Pneumocystis jirovecii* pneumonia, babesiosis, infections with West Nile virus, and cytomegalovirus [1,15]. Some of the bacterial infections associated with the use of rituximab described in the literature are *Staphylococcus warneri* meningitis with *Strongyloides stercoralis* superinfection in a patient with mantle cell lymphoma and tracheobronchitis caused by *Pasteurella multocida* in a patient with chronic lymphocytic leukemia [16,17]. Both patients were treated with rituximab as maintenance therapy. In patients with non-Hodgkin’s lymphoma who were treated with rituximab as a maintenance therapy and who had developed different degrees of hypogammaglobulinemia, staphylococci and *Escherichia coli* were reported as causes of bacterial infections [13]. In another study, 20% of patients treated with rituximab and chemotherapy developed infections without neutropenia. In all cases in which electrophoresis of serum proteins was performed, different degrees of hypogammaglobulinemia were observed. These patients were successfully treated with intravenous gamma globulins [18].

Here we have presented a patient who developed severe hypogammaglobulinemia after only 6 cycles of rituximab, for whom infection occurred 40 days after the last cycle. Besides application of rituximab, the potential risk factors were underlying lymphoproliferative disease and immunosuppressive therapy usage. Although rituximab is a safe drug for use, further research is necessary about its use in certain groups of patients who might develop an opportunistic infection. Controlling the value of gamma globulins during rituximab therapy might reduce the number of infections by temporary interruption of rituximab or by giving prophylactic intravenous gamma globulins in cases of severe hypogammaglobulinemia. Expansion of indications for rituximab use and increasing duration of treatment with rituximab will certainly bring about more opportunistic infections, such as those caused by *Leuconostoc*.

**Conflict of Interest Statement**

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

**References**

1. Gea-Banacloche JC. Rituximab-associated infections. Semin Hematol 2010;47:187-198.
2. Lehman DC, Mahon CR, Suvarna K. *Streptococcus*, *Enterococcus* and other catalase-negative gram-positive cocci. In: Mahon CR, Lehman DC, Manuselis G, (eds). Textbook of Diagnostic Microbiology, 3rd ed. St. Louis, Saunders Elsevier, 2007.
3. Ruoff KL. *Leuconostoc, Pediococcus, Stomatococcus* and miscellaneous gram-positive cocci that grow aerobically. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH (eds). Manual of Clinical Microbiology, 7th ed. Washington DC, American Society for Microbiology, 1999.
4. Janow G, Lambert B, Scheiner M, Rosen O, Goldman DL, Soghier L. *Leuconostoc* septicemia in a preterm neonate on vancomycin therapy: case report and literature review. Am J Perinatol 2009;26:89-91.
5. Yossuck P, Miller-Canfield P, Moffett K, Graeber J. *Leuconostoc* spp. sepsis in an extremely low birth weight infant: a case report and review of the literature. W V Med J 2009;105:24-27.
6. Handwerger S, Horowitz H, Coburn K, Kolokathis A, Wormser GP. Infection due to *Leuconostoc* species: six cases and review. Rev Infect Dis 1990;12:602-610.
7. Florescu D, Hill L, Sudan D, Iwen PC. *Leuconostoc* bacteremia in pediatric patients with short bowel syndrome: case series and review. Pediatr Infect Dis J 2008;27:1013-1019.
8. Friedland IR, Snipelisky M, Khoosal M. Meningitis in a neonate caused by *Leuconostoc* sp. J Clin Microbiol 1990;28:2125-2126.
9. Coovadia YM, Solwa Z, van den Ende J. Meningitis caused by vancomycin-resistant *Leuconostoc* sp. J Clin Microbiol 1987;25:1784-1785.
10. Starr JA. *Leuconostoc* species-associated endocarditis. Pharmacotherapy 2007;27:766-770.
11. Deye G, Lewis J, Patterson J, Jorgensen J. A case of *Leuconostoc* ventriculitis with resistance to carbapenem antibiotics. Clin Infect Dis 2003;37:869-870.
12. Aksoy S, Dizdar O, Hayran M, Harputluoglu H. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. Leuk Lymphoma 2009;50:357-365.

13. Azad A, Campbell P. High rates of infection associated with the use of maintenance rituximab monotherapy in non-Hodgkin lymphoma. Intern Med J 2009;39:778-779.

14. Rafailidis PI, Kakisi OK, Vardakas K, Falagas ME. Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials. Cancer 2007;109:2182-2189.

15. Ganjoo KN, Raman R, Sobel RA, Pinto HA. Opportunistic enteroviral meningoencephalitis: an unusual treatable complication of rituximab therapy. Leuk Lymphoma 2009;50:673-675.

16. Incani RN, Hernández M, Cortez J, González ME, Salazar YD. Staphylococcus warneri meningitis in a patient with Strongyloides stercoralis hyperinfection and lymphoma: first report of a case. Rev Inst Med Trop Sao Paulo 2010;52:169-170.

17. Deming D, Silverman E. Pasteurella multocida tracheobronchitis in a patient with CLL on rituximab. Am J Hematol 2010;85:144-145.

18. Cabanillas F, Liboy I, Pavia O, Rivera E. High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication. Ann Oncol 2006;17:1424-1427.