



## A Different Facilitating Factor in the Etiology of Meningitis

Gamze Gursoy<sup>1\*</sup>, Caglayan Merve Ayaz<sup>2</sup>, Oguz Kodaz<sup>3</sup> and Serhat Unal<sup>4</sup>

<sup>1</sup>Department of Infectious Diseases, Ardahan State Hospital, Turkey

<sup>2</sup>Department of Infectious Diseases and Clinical Microbiology, Ankara City Hospital, Turkey

<sup>3</sup>Department of Nuclear Medicine, Hacettepe University, Turkey

<sup>4</sup>Department of Infectious Diseases and Clinical Microbiology, Hacettepe University, Turkey

### Abstract

Bacterial meningitis is a rare infectious disease with high morbidity and mortality. Usually there are facilitating factors such as head trauma or previous head surgery. In this case, extra nodal marginal zone lymphoma was shown as the underlying facilitating factor in a patient who was followed up with the diagnosis of meningitis. Although 1% of all non-Hodgkin's lymphomas present with orbital involvement. Lymphomas inactivating the complement pathway, particularly the alternative pathway, may cause an increase in the sensitivity of gram-negative bacteria. In this case, although no causative agent could be produced in the culture, gram-negative bacteria were observed in the microscopic smear, and empirical antibiotic therapy was started considering the clinical findings, and clinical improvement was observed.

**Keywords:** Gram-negative bacteria; Non-Hodgkin lymphoma; Bacterial meningitis; Cerebrospinal fluid

### Introduction

Bacterial meningitis is a rare infectious disease with high morbidity and mortality [1]. Common pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*. Gram-Negative Bacteria (GNB) are rarely encountered in the etiology, usually there are facilitating factors such as head trauma or previous head surgery [2]. Marginal zone lymphomas are CD20 (+), low grade and B cell origin Non-Hodgkin Lymphomas (NHL) [3]. In this case, extra nodal marginal zone lymphoma was shown as the underlying facilitating factor in a patient who was followed up with the diagnosis of gram-negative meningitis.

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#### \*Correspondence:

Gamze Gursoy, Department of Infectious Diseases, Ardahan State Hospital, Ardahan, Turkey, Tel: 05378264113;

E-mail: gamzegursoy@hacettepe.edu.tr

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### Case Presentation

The patient was 79 years old, female, not working, living in Ankara with two children. She had hypertension (diagnosed 15 years ago, using metoprolol 25 mg, lercanidipine 20 mg), cholelithiasis, and previous stroke history (using clopidogrel 75 mg). Before admission to our hospital, she was admitted to the other medical center with the signs and symptoms of fever, blurred consciousness, back and neck pain. No pathology was detected in brain imaging performed due to possible cerebrovascular attack. In examination of other systems, no pathology was found to explain the patient's situation. Meropenem, linezolid, piperacillin-tazobactam and levofloxacin treatments were given with possible sepsis for three days in other center, and then the patient was referred to our clinic for further evaluation. Her consciousness was still blurred on admission. On physical examination, nuchal rigidity, Kernig's and Brudzinski's signs were positive. She had still fever (39.0°C) but no hypotension was seen. Due to her back pain, direct lumbar and sacral radiographies were performed, no pathology was detected. Complete blood count was normal except for normochrome macrocytic anemia. Blood sodium and uric acid levels were consistent with inappropriate antidiuretic hormone syndrome. Complete urine analysis revealed no pyuria, together with blood and urine cultures were sterile. No pathology was found in the chest radiography taken to exclude other possible causes of fever. There were no findings in favor of new onset stroke on brain Computed Tomography (CT) and brain Magnetic Resonance Imaging (MRI). However, imaging methods revealed a mass behind the left eye that did not erode the paranasal sinuses (Figure 1, 2).

Lumbar puncture was performed and Cerebrospinal Fluid (CSF) aerobic culture was sent, direct microscopy was performed. Microscopy showed the presence of Gram-Negative Bacilli (GNB) whereas CSF culture was resulted negative. Laboratory parameters of patient were shown in Table 1.

**Table 1:** Blood and CSF results of patient.

Blood Test Results		Range
Sodium	129 mEq/L	(136-146 mEq/L)
Chloride	94 meq/L	(101-109 mEq/L)
Uric acid	1.86 mEq/L	(2.6-6 mEq/L)
CRP	7.3 mg/dL	(0-0.8 mg/dL)
CSF Test Results		Range
Protein	183.8 mg/dL	(15-40 mg/dL)
Glucose	52 mg/dL	(concurrent blood glucose was: 83 mg/dL)

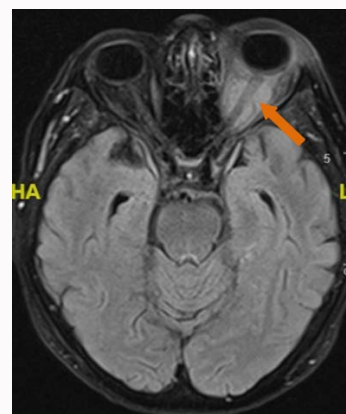
**Figure 1:** Intracranial extension of mass around the optic nerve in the left orbit (brain CT).

Empirical meropenem treatment was started because of possible meningitis in the patient who had fever and blurred consciousness with the result of microscopy. Meropenem treatment completed in 14 days. Low back pain completely disappeared during follow-up, blurred consciousness improved and fever declined. Excision biopsy was performed with orbitotomy from the mass after the treatment of meningitis was completed. Histopathological examination was performed from the mass seen behind the eye in imaging methods. The result of the examination was reported as marginal zone lymphoma, which was one of the NHL. For staging of the lymphoma, the patient underwent full-body imaging, no involvement was found at any other location, and chemotherapy was planned by oncology department.

## Discussion

Non-Hodgkin lymphoma is a neoplasm of lymphoid tissue [4]. Although 1% of all NHLs present with orbital involvement [5], lymphomas are the most common orbital involvement in patients 60 years and older [6]. Complement systems are a complex protein network and are an integral part of innate immunity [7]. The alternative complement pathway is an important pathway for killing encapsulated GNB [8]. One study demonstrated that the expression of complement-dependent cytotoxicity inhibitors (CD55, CD59) in NHL cells [9]. Inhibition of the complement pathway, particularly the alternative pathway, may cause an increase in the sensitivity of infections with encapsulated GNB [7].

It was interesting that the patient was diagnosed with lymphoma by brain imaging performed to rule out new stroke attack. The mass behind the eye was not noticed even though the patient underwent brain imaging in the external center. This means that a good radiological evaluation is more important than radiological imaging

**Figure 2:** Appearance of existing mass at different levels in T2 sequence imaging (brain MRI).

in diagnosis. It was understood that even if the patient has increased sensitivity to infectious with encapsulated GNB due to advanced age, the etiology of spontaneous bacterial meningitis and the presence of other facilitating factors may need to be investigated.

According to the World Health Organization meningitis diagnosis and treatment guideline, the patient's clinical findings, CSF protein >45 mg/dl, and gram-negative bacilli in gram staining were supported the diagnosis of meningitis [10]. In this case, although no causative agent could be produced in the culture, GNB were observed in the microscopic smear. Empirical antibiotic therapy was started considering the clinical findings, after initiation of antibiotic treatment, clinical improvement was observed. The patient's lack of benefit despite receiving antibiotic treatments in the first medical center where she applied was attributed to the fact that the drugs were not given at the meningitis dose. Among the reasons for giving meropenem as an empirical treatment were 1) the patient's recent exposure to broad-spectrum antibiotics and 2) the absence of an antibiogram result due to the inability to grow the bacteria in cultured which was seen in microscopy. Additionally, the most logical explanation for the inability to grow the GNB in culture was thought to be the previous antibiotic treatments that the patient had taken.

## Conclusion

In older patients, signs of meningitis may be faint and bacterial growth may not always be detected in culture. When the diagnosis of gram-negative meningitis is made in older patients, it should be investigated whether there are other underlying facilitating factors. Microscopic smear should be done with CSF culture for each patient, must be combined with signs and symptoms. In conclusion, clinician's opinion and microscopic examination are very essential in the diagnosis of meningitis in older patients.

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