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Vancomycin-resistant *Enterococcus faecium*-associated encephalitis and concurrent cerebellitis

Case Report

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Abstract: Enterococci are uncommon etiologic agents of central nervous system infections. We describe a case of nosocomial encephalitis and concurrent cerebellitis associated with *Enterococcus faecium* in a man, with extranodal natural killer/T-cell lymphoma, nasal type, who underwent high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Brain magnetic resonance images showed lesions in the bihemispheral cerebellar cortex with swelling and several small lesions in both cerebral hemispheres. The blood and cerebrospinal fluid cultures were positive for vancomycin-resistant *E. faecium*. Vancomycin-resistant *E. faecium* can cause encephalitis and concurrent cerebellitis in an immunocompromised patient who underwent autologous peripheral blood stem cell transplantation.

Keywords: *Cerebellitis • Encephalitis • Enterococcus faecium • Vancomycin • Magnetic resonance imaging • Peripheral blood stem cell transplantation • Extranodal NK-T-cell lymphoma.*

1. Introduction

Encephalitis is an acute inflammation of the brain parenchyma and presents as fever, headache, seizures, and an alteration in consciousness [1,2]. Infectious causes of acute encephalitis are myriad [1-8]. However, a specific etiology is identified in less than one-third of cases, even if extensive laboratory testing is performed [2]. Encephalitis is most commonly caused by viruses such as herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein–Barr virus, enteroviruses, and lymphocytic choriomeningitis virus [1,2,8]. Other microorganisms that can cause encephalitis include protozoa, such as *Toxoplasma gondii*, and bacteria, such as *Mycoplasma pneumoniae, Haemophilus influenzae, Neisseria meningitides*, and groups A and B streptococci [1-3,8]. Syphilis, bartonellosis, borreliosis, brucellosis, leptospirosis, tuberculosis, and listeriosis are other

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bacterial infections that can be associated with encephalitis [1,2,8].

Enterococci are uncommon etiologic agents of central nervous system infections [9]. Enterococcal meningitis tends to occur in patients with chronic medical conditions that are often associated with immunosuppressive therapy, underlying central nervous system disease, and gastrointestinal pathology [9]. To our knowledge, encephalitis with cerebellar involvement has never been reported in enterococcal central nervous system infection. Here we describe a case of encephalitis and concurrent cerebellitis associated with *Enterococcus faecium* in a patient with extranodal natural killer/T-cell lymphoma, nasal type who underwent autologous peripheral blood stem cell transplantation.

2. Case Report

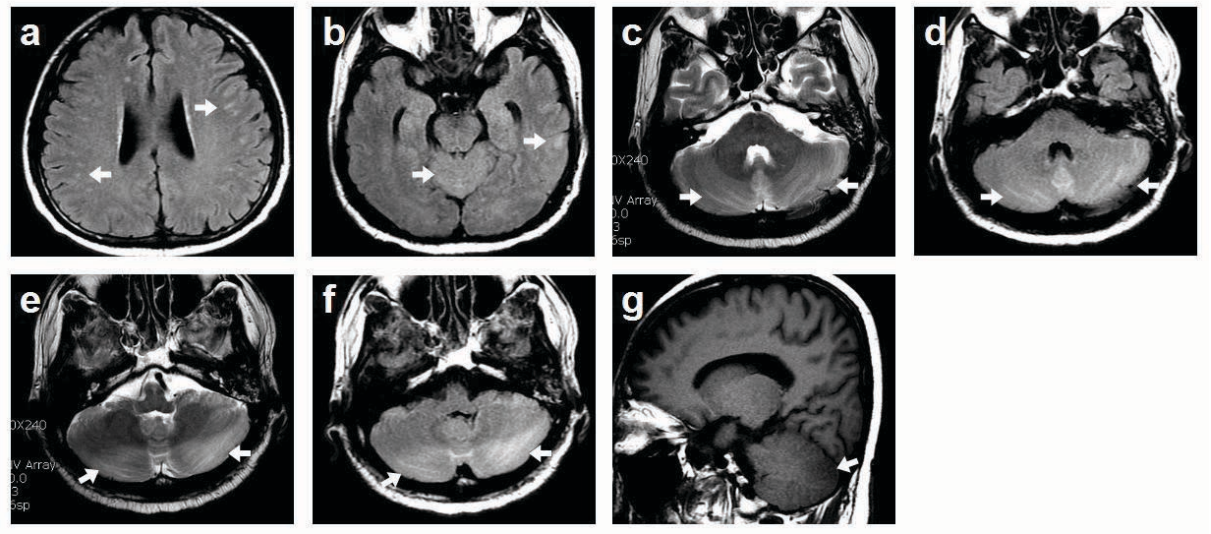
A 40-year-old man detected a mass in the right nasal cavity in September of 2005. Histological findings from the mass led to a diagnosis of extranodal natural killer/T-cell lymphoma, nasal type. After four cycles of initial treatment with ifosfamide, methotrexate, etoposide and prednisolone chemotherapy, the patient received irradiation of the nasal cavity (50 Gy). He achieved complete remission in April of 2006. In October of 2006, the patient developed masses in the left maxillary area and the left forearm. He was therefore re-admitted to our hospital and was given two cycles of second-line chemotherapy treatment consisting of dexamethasone, cytarabine and cisplatin, but the cutaneous lymphoma lesions remained. In February of 2007, the patient had autologous peripheral blood stem cells transplanted. A neutrophil count >500/μl was achieved 10 days after his first autologous peripheral blood stem cells transplantation. He was discharged on March 14, 2007, and later in the month he developed necrotic cutaneous lesions on the left nose.

On April 10, 2007, the patient was admitted to our hospital again. Histology of the nasal lesion revealed proliferation of atypical lymphocytes. He was therefore placed on combination chemotherapy consisting of cytarabine, etoposide, cisplatin and L-asparagenase. Cytarabine was infused in doses of 2g/m^2 every 12 hours on days 9, 14, 16, and 18 of hospitalization. He was also given piperacillin-tazobactam and fluconazole for intermittent fever. On day 17, the patient received tandem autologous peripheral blood stem cells transplantation.

On day 28, he became agitated and disoriented, and his speech was dysarthric. On day 32, he developed recurrent seizures and a declining mental status. During a seizure, he cried out, resisted and struck out at the staff with irregular respiration, transient mydriasis and version of the eyes to the left side. During the interictal periods, he did not respond to his name being called or to being shaken. A moan and grimace was provoked by painful stimuli. While grimacing in response to the stimuli, facial weakness was not observed. The pupils reacted normally to light. The doll's eye maneuver easily elicited full and conjugate deviation of the eyes. Noxious stimuli gave rise to extensor postures of the arms and flexor responses of the legs. Plantar responses were bilaterally extensor. His neck was rigid. At this time, a white blood cell (WBC) count was found to be 300/μl. On day 33, he developed a fever rising to 39.0°C and underwent a lumbar puncture. The opening pressure was 140 mmH_2O, and analysis of cerebrospinal fluid (CSF) revealed the following measurements: WBC count, 0/μl; red blood cell (RBC) count, 3/μl; glucose level, 50 mg/dl (simultaneous serum glucose level was unavailable.); protein level, 120.3 mg/dl. A CSF examination demonstrated negative polymerase chain reaction and culture for herpesviruses (herpes simplex virus type 1 and 2, varicella-zoster virus, and cytomegalovirus). Cryptococcal, pneumococcal, meningococcal, and *H. influenzae* antigens were not found in the CSF. On Gram stain and culture of the CSF, no organisms were identified. Malignant cells were also not found in the CSF. Gram-positive cocci were seen in Gram-stained smears of blood cultures drawn from the Hickman catheter and peripheral veins. A C-reactive protein level was 20.6 mg/L. The patient was given vancomycin, imipenem and amphotericin. On day 35, imipenem therapy was discontinued, and the patient was started on intravenous phenytoin for the recurrent seizures. On day 36, the C-reactive protein level rose to 338.1 mg/L. A magnetic resonance imaging (MRI) scan was performed and several small hyperintense lesions were found on fluid-attenuated inversion recovery (FLAIR) images of both cerebral hemispheres (Figure 1). In addition, the MRI revealed lesions in both hemispheres of the cerebellar cortex, hypointense on T1-weighted images and hyperintense on T2-weighted and FLAIR images, with cerebellar swelling (Figure 1). The patient was given acyclovir for possible viral encephalitis. Electroencephalograms showed generalized abnormalities characterized by slow background rhythms. Intravenous sodium valproate was added to the treatments regimen at this time.

On day 37, the results of the blood cultures drawn on day 33 were reported. Bacterial identification was performed using a rapid motility test [10] and GPI cards of the VITEK system (BioMerieux, Hazelwood, USA). Resistance against antimicrobial agents was confirmed

Figure 1. A brain magnetic resonance imaging (MRI) scan was performed on day 36 of hospitalization. Fluid-attenuated inversion recovery (FLAIR) images showed several small hyperintense lesions in both cerebral hemispheres (a, b). In addition, brain MRI demonstrated lesions in both hemispheres of the cerebellar cortex slightly hyperintense on T2-weighted (c, e) and FLAIR (b, d, f) images and hypointense on T1-weighted images with swelling (g).



by determining minimum inhibitory concentrations using E-test (AB Biodisk, Piscataway, USA). The blood cultures were positive for vancomycin resistant *E. faecium*. The isolate was found to be resistant to ampicillin, rifampicin, ciprofloxacin, norfloxacin, and vancomycin, and sensitive to teicoplanin, linezolid, quinupristine-dalfopristin and tetracycline. Blood was again drawn from the Hickman catheter and peripheral veins, and Gram-positive cocci were again seen in stained blood smears. As soon as the results of blood cultures were reported, the patient was started on linezolid, and vancomycin was discontinued. A rectal swab culture was performed and was found negative for vancomycin-resistant enterococcus (VRE). On day 37, follow-up CSF analysis revealed the following measurements: WBC count, 1/µl; RBC count, 135/µl; glucose level, 50 mg/dl (simultaneous serum glucose level was unavailable.); and protein level, 120.3 mg/dL. On neurological examination, both pupils dilated and were sluggish to light. The doll's eye maneuver elicited neither vertical nor horizontal eye movements. A flaccid quadriplegia was seen and plantar responses were bilaterally flexor.

On day 42, the result of the follow-up CSF culture was reported. The CSF culture was positive for vancomycin-resistant *E. faecium*. The patient died on day 42 of hospitalization. After his tandem autologous peripheral blood stem cells transplantation, a neutrophil count >500/µl was never achieved. An autopsy was not performed because the family of the patient did not agree.

3. Discussion

We believe that *E. faecium* was the pathogen responsible for this case of acute encephalitis with concurrent cerebellitis. There might be a possibility that the encephalitis was not caused by VRE and that infected blood was introduced to the central nervous system as a result of traumatic lumbar puncture, leading to the positive result of the CSF culture. The patient was bacteremic and the initial CSF was sterile with a normal glucose level and a normal WBC count. The follow-up lumbar puncture yielded CSF with 135 RBCs/µl and VRE grew from this CSF. A lumbar puncture can be considered traumatic, if more than 400-1000 RBCs/µl are present [11]. However, our patient had lower numbers of RBCs in the CSF. Thus, there were no traumatic taps, and introduction of infected blood seems an unlikely explanation for the positive CSF culture result [12].

Then, why did our patient have sterile initial CSF with normal CSF glucose level and low CSF leukocyte count? We can suggest several possible explanations. First, enterococcal meningitis is usually associated with low CSF leukocyte counts [13]. Second, our patient was severely immunocompromised and a normal CSF leukocyte count can be seen in immunocompromised subjects [14]. Third, our patient was receiving solutions of dextrose at the time of the lumbar puncture. Thus, serum glucose level might have been very high, and resultantly, a CSF-to-serum glucose ratio might have been low if we had checked serum glucose level at the time of lumbar puncture. Fourth, the fact that our patient

was receiving antibiotics at the time of initial lumbar puncture may explain why the initial CSF was sterile. The probability of identifying the organism on Gram stain and culture of CSF can decrease in patients who have received prior antimicrobial therapy [14]. In addition, the CSF protein concentration was already elevated on the initial lumbar puncture, which indicates that the CSF was already abnormal before the initial lumbar puncture in our case.

Cerebellar toxicity related to systemic administration of high-dose cytarabine is a well-recognized entity and might be another differential diagnosis in our case [15,16]. However, this diagnosis was excluded by both the clinical setting and the MRI findings. First, the acute cerebellar syndrome following cytarabine usually appears between the third and seventh day after starting the chemotherapy [15]. However, our patient developed his symptoms 19 days after the initiation of the chemotherapy. Second, the MRI findings of our patient are quite different from previously reported MRI findings of acute cerebellar toxicity. French investigators reported a patient with acute cerebellar toxicity, which manifested bilateral diffuse lesions in the deep white matter of the cerebellar hemispheres [16]. In contrast, our patient had bilateral lesions in the cerebellar cortex.

MRI is more sensitive and specific and provides more detailed diagnostic information than computed tomography in patients with suspected encephalitis, and is the imaging technique of choice when available [1,2]. Different forms of encephalitis can produce distinctive patterns of neuroimaging abnormalities that provide clues suggestive of particular pathogens, which can guide more definitive tests such as polymerase chain reaction, antibody tests, and brain biopsy [1,2]. Concurrent cerebellitis with encephalitis is unusual and has been reported to occur in association with Japanese encephalitis virus, Influenza A virus, rotavirus, and herpes simplex virus [4-7]. The association of VRE with encephalitis and concurrent cerebellitis has rarely been documented.

Enterococci occur naturally among the normal flora in the human gastrointestinal tract [9]. Initially thought to be harmless commensal organisms in hospitalized patients, enterococci have emerged as significant nosocomial pathogens [9]. Enterococcal infections are a major cause of significant morbidity following high-dose chemotherapy with autologous peripheral blood stem cell transplantation [17]. A substantial period of immunologic dysfunction follows high-dose chemotherapy with autologous peripheral blood stem cell transplantation, including a period of profound neutropenia immediately following autologous stem cell infusion [17]. However, enterococci are uncommon etiologic agents of bacterial meningitis. In a review of 151 cases of nosocomial meningitis, enterococci accounted for only 3% of the cases [18]. The presumed pathogenesis is enterococcal bacteremia originating from the gastrointestinal tract with secondary seeding of the meninges [9]. Although the typical presentation of enterococcal meningitis is rapid onset of fever, signs of meningeal irritation, and altered sensorium, subacute presentation has been described [19,20]. The mortality rate of patients with enterococcal meningitis is high, ranging from 13% to 33% [9]. Most cases of enterococcal meningitis are caused by *Enterococcus faecalis* [9]. *E. faecium* is responsible for only 10% of the cases of enterococcal meningitis, but it poses a treatment challenge, because the rates of resistance to ampicillin and vancomycin are increasing [9]. Enterococci are intrinsically resistant to several antibiotics and possess the ability to acquire resistance through the exchange of genetic material [21]. As a result, they have become more resistant to multiple antibiotics [9]. For enterococci resistant to both vancomycin and β-lactams, no established therapies provide uniformly bactericidal activity [22]. Two agents active against VRE infection are linezolid and daptomycin [22,23].

The case reported demonstrates the difficulty in treating patients with VRE infection following high-dose chemotherapy with autologous peripheral blood stem cell transplantation. The patient did not respond to systemic antibiotics and died as a consequence of the VRE infection. The incidence of VRE is increasing and the nosocomial spread of VRE in transplant units is a potentially serious problem [24]. To prevent nosocomial infections, precautions directed against VRE contamination remain the only effective measure [24].

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References

[1] Beckham J. D., Tyler K. L., Encephalitis, In: Mandell G. L., Bennett J. E., Dolin R., (Eds.), Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed., Churchill Livingstone/ Elsevier, Philadelphia, 2010

[2] Willoughby Jr. R. E., Long S. S., Encephalitis, meningoencephalitis, acute disseminated encephalomyelitis, and acute necrotizing encephalopathy, In: Long S. S., Pickering L. K., Prober C. G., (Eds.), Principles and practice of pediatric infectious diseases. 3rd ed., Churchill Livingstone/Elsevier, Philadelphia, 2008

[3] Yang T. H., Jeong S. Y., Oh S. Y., Shin B. S., Seo M. W., Kim Y. H., et al., Recurrent Streptococcus Pneumoniae meningoencephalitis in a patient with a transethmoidal meningoencephalocele, J Clin Neurol, 2008, 4, 40-44

[4] Fluss J., Ferey S., Menache-Starobinski C., Delavelle J., Van Bogaert P., Vargas M. I., Mild influenza-associated encephalopathy/encephalitis with a reversible splenial lesion in a Caucasian child with additional cerebellar features, Eur J Paediatr Neurol, 2010, 14, 97-100

[5] Shiihara T., Watanabe M., Honma A., Kato M., Morita Y., Ichiyama T., et al., Rotavirus associated acute encephalitis/encephalopathy and concurrent cerebellitis: report of two cases, Brain Dev, 2007, 29, 670-673

[6] Ohta K., Funaki M., Tanaka M., Suzuki N., Early cerebellar involvement on diffusion-weighted magnetic resonance images in herpes simplex encephalitis, J Neurol, 1999, 246, 736-738

[7] Misra U. K., Kalita J., Movement disorders in Japanese encephalitis, J Neurol, 1997, 244, 299-303

[8] Granerod J., Cunningham R., Zuckerman M., Mutton K., Davies N. W., Walsh A. L., et al., Causality in acute encephalitis: defining aetiologies, Epidemiol Infect, 2010, 138, 783-800

[9] Zeana C., Kubin C. J., Della-Latta P., Hammer S. M., Vancomycin-resistant Enterococcus faecium meningitis successfully managed with linezolid: case report and review of the literature, Clin Infect Dis, 2001, 33, 477-482

[10] Hanson K. L., Cartwright C. P., Comparison of simple and rapid methods for identifying enterococci intrinsically resistant to vancomycin, J Clin Microbiol, 1999, 37, 815-817

[11] Shah K. H., Richard K. M., Nicholas S., Edlow J. A., Incidence of traumatic lumbar puncture, Acad Emerg Med, 2003, 10, 151-154

[12] Teele D. W., Dashefsky B., Klein J. O., Meningitis after lumbar puncture in children with bacteremia, N Engl J Med, 1982, 306, 608-610

[13] Bayer A. S., Seidel J. S., Yoshikawa T. T., Anthony B. F., Guze L. B., Group D enterococcal meningitis. Clinical and therapeutic considerations with report of three cases and review of the literature, Arch Intern Med, 1976, 136, 883-886

[14] Tunkel, A. R., Scheld, W. M., Acute meningitis, In: Mandell G. L., Bennett J. E., Dolin R., (Eds.), Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed., Churchill Livingstone/Elsevier, Philadelphia, 2010

[15] Herzig R. H., Hines J. D., Herzig G. P., Wolff S. N., Cassileth P. A., Lazarus H. M., et al., Cerebellar toxicity with high-dose cytosine arabinoside, J Clin Oncol, 1987, 5, 927-932

[16] Yeshurun M., Marsot Dupuch K., Acute cerebellar syndrome following intermediate-dose cytarabine, Br J Haematol, 2001, 113, 846

[17] Kapur D., Dorsky D., Feingold J. M., Bona R. D., Edwards R. L., Aslanzadeh J., et al., Incidence and outcome of vancomycin-resistant enterococcal bacteremia following autologous peripheral blood stem cell transplantation, Bone Marrow Transplant, 2000, 25, 147-152

[18] Durand M. L., Calderwood S. B., Weber D. J., Miller S. I., Southwick F. S., Caviness V. S., Jr., et al., Acute bacterial meningitis in adults. A review of 493 episodes, N Engl J Med, 1993, 328, 21-28

[19] Stevenson K. B., Murray E. W., Sarubbi F. A., Enterococcal meningitis: report of four cases and review, Clin Infect Dis, 1994, 18, 233-239

[20] Brown D. R., Reichman R. C., Enterococcal meningitis: a subacute presentation, N Y State J Med, 1989, 89, 92-93

[21] Huycke M. M., Sahm D. F., Gilmore M. S., Multiple-drug resistant enterococci: the nature of the problem and an agenda for the future, Emerg Infect Dis, 1998, 4, 239-249

[22] Wessels M. R., Streptococcal and enterococcal infections, In: Fauci A. S., Braunwald E., Kasper D. L., Hauser S. L., Longo D. L., Jameson J. L., et al., (Eds.), Harrison's principles of internal medicine. 17th ed., McGraw-Hill, New York, 2008

[23] Levine D. P., Clinical experience with daptomycin: bacteraemia and endocarditis, J Antimicrob Chemother, 2008, 62 Suppl 3, iii35-39

[24] Koc Y., Snydman D. R., Schenkein D. S., Miller K. B., Vancomycin-resistant enterococcal infections in bone marrow transplant recipients, Bone Marrow Transplant, 1998, 22, 207-209