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Tuberculous Meningitis-Mimicking Varicella-Zoster Meningitis

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Background: Varicella-zoster virus (VZV) is one of the most common etiologies of aseptic meningitis. The severest manifestation of VZV meningitis is occasionally confused with tuberculous meningitis (TBM). Thus, we investigated the clinical manifestations of VZV meningitis as compared with those of TBM.

Materials and Methods: All adult patients who were diagnosed with VZV meningitis or TBM were enrolled at a tertiary hospital in Seoul, South Korea, during an 8-year period. The clinical characteristics and cerebrospinal fluid (CSF) profile of patients were analyzed.

Results: Seventy-nine patients with VZV meningitis and 24 patients with TBM were enrolled in this study. Of the 79 patients with VZV meningitis, 63 (80%) did not received empirical anti-tuberculous therapy (Group 1) and the remaining 16 (20%) received empirical anti-tuberculous therapy (Group 2), compared with 24 patients with TBM (Group 3). Altered mental status, intensive care unit (ICU) admission, neurologic sequelae, CSF protein levels, and CSF adenosine deaminase levels revealed a trend of being higher in Group 3 than Group 2, which was higher than Group 1. However, the CSF/serum glucose ratio was significantly lower in Group 3 than in Group 1 or Group 2.

Conclusion: About one fifth of VZV meningitis cases presented as severe manifestations, mimicking TBM. The CSF/serum glucose ratio might be useful to differentiate VZV meningitis from TBM until definite diagnostic tests are available. Physicians should keep in mind that a differential diagnosis between severe VZV meningitis and TBM is needed.

Key Words: Herpesvirus 3, Human; Tuberculosis, Meningeal

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Introduction

Varicella-zoster virus (VZV) is an α-herpesvirus with the ability to establish latency in dorsal-root ganglia or cranial-nerve ganglia. Central nervous system (CNS) manifestations can follow both primary infection or reactivation by VZV and occur without concomitant skin rash in up to a third to half of patients, referred to as "zoster sine herpete" [1, 2]. The spectrum of CNS diseases caused by this virus is broad, ranging from self-limiting aseptic meningitis to encephalitis, causing death and disability. The cerebrospinal fluid (CSF) profile of VZV meningitis is lymphocytic pleocytosis and significantly higher protein levels than those of enterovirus meningitis [3]. Therefore, the severest manifestation of VZV meningitis is occasionally confused with tuberculous meningitis (TBM), especially in tuberculosis (TB) endemic areas. However, there are limited data on TBM-mimicking VZV meningitis. The purpose of this study was to compare the clinical characteristics of patients with VZV meningitis to those with TBM in an intermediate TB burden country.

Materials and Methods

1. Patient selection, Definitions and diagnostic criteria of CNS infection

This retrospective study was performed at Asan Medical Center: a 2,700-bed tertiary hospital in Seoul, South Korea. All adults (age 16 years) who were diagnosed with VZV meningitis or TBM between 2008 and 2015 were enrolled. The definition and diagnostic criteria of CNS infection were previously described [4, 5]. A case of meningitis was defined as CSF white blood cell (WBC) count >5 cell/mm^3 and negative bacterial culture from CSF without acute signs of parenchymatous brain dysfunctions and with two or more of the following finding: headache, nausea/vomiting, photophobia, neck stiffness, and fever >38℃. A case of encephalitis was defined as encephalopathy (depressed or altered level of consciousness lasting over 24hr, lethargy, or change in personality) and one or more of the following findings: fever, seizure, focal neurologic deficit, CSF WBC count >5 cell/mm^3, and electroencephalogram abnormality or neuroimaging report consistent with encephalitis.

Patients whose clinical presentation was indicative of CNS infection and who had a positive CSF PCR result for VZV were considered to have had confirmed VZV CNS infections. Patients whose clinical presentation was indicative of CNS infection were considered to have confirmed TBM if CSF specimens were found to have lymphocytic pleocytosis, raised protein levels, and sterile cultures, as well as if CSF specimens were found to be positive for *Mycobacterium tuberculosis* in culture or by polymerase chain reaction (PCR) assay [6, 7]. Patients whose clinical presentation was indicative of CNS infection plus a positive culture of *M. tuberculosis* in other body fluids without other known etiologies of meningitis were considered to have had probable TBM [6].

2. Statistical analysis

All statistical analyses were carried out using SPSS version 21.0 (SPSS, Chicago, IL, USA). Categorical variables were compared by Fisher's exact test or Pearson chi-square test, as appropriate. Continuous variables were compared using the Mann-Whitney *U*-test or Student's *t*-test. The Jonckheere-Terpstra test was performed to determine whether or not there was a trend among CSF profiles of patients in all three groups: patients with VZV meningitis who did not receive empirical anti-tuberculous therapy (Group 1), patients with VZV meningitis who received empirical anti-tuberculous therapy (Group 2), and patients with TBM (Group 3). The association of clinical characteristics between groups was analyzed by Linear-by-Linear Association test. All tests were two-tailed and differences were considered significant at P <0.05.

3. Ethics statement

The study was approved by the Institutional Review Board of Asan Medical Center (No. 2016-1313) and the requirement for informed consent was waived because of the retrospective nature of the study.

Results

1. Patient characteristics

A total of 103 patients were identified during an 8-year period. Seventy-nine patients were diagnosed with VZV meningitis and 24 patients were diagnosed with TBM. Of the 24 patients with TBM, 22 (92%) patients were classified as confirmed TB (20 positive CSF culture for M. TB and 2 positive CSF PCR test) and 2 (8%) patients as probable TB. Sex differences were observed in patients with VZV meningitis and TBM, with female predominance in TBM (VZV meningitis, 60% male *vs.* TBM, 25% male; P <0.01). The time interval between onset of symptoms and CSF examination was 4 days (Interquartile range [IQR], 3.0 – 7.0) in patients with VZV men-

Table 1. Clinical characteristics and outcomes in patients with central nervous system infections caused by varicella-zoster virus and *Mycobacterium tuberculosis*

	VZV (n = 79)	TB (n = 24)	*P*-value
Demographics			
Age, median years (IQR)	36 (28-62)	47 (42.25-55)	0.09
Male, n (%)	47 (60)	6 (25)	0.003
Underlying disease, n (%)			
None	58 (73)	17 (71)	0.80
Diabetes mellitus	7 (9)	4 (17)	0.28
Solid organ transplantation	2 (3)	0	>0.99
HSCT	3 (4)	0	>0.99
Solid cancer	2 (3)	0	>0.99
Immunocompromised[a]	2 (3)	2 (8)	0.23
Others	6 (8)	3 (13)	0.43
Clinical manifestations, n (%)			
Headache	73 (92)	22 (92)	>0.99
Fever	60 (76)	22 (92)	0.15
Nausea/vomiting	43 (54)	5 (21)	0.004
Neck stiffness	43 (54)	16 (67)	0.29
Cutaneous zoster	26 (33)	0	0.001
Ear vesicle	7 (9)	0	0.19
Altered mental status	12 (15)	17 (71)	<0.001
Seizure	2 (3)	5 (21)	0.007
Coma	0	1 (4)	0.23
Clinical diagnosis, n (%)			
Meningitis	64 (81)	8 (33)	<0.001
Encephalitis	15 (19)	16 (67)	
Cranial nerve affection	13 (17)	3 (13)	0.76
Ramsay - Hunt syndrome	10 (13)	0	0.11
Course of illness			
ICU hospitalization, n (%)	8 (10)	10 (42)	0.001
Assisted ventilation, n (%)	3 (4)	6 (25)	0.005
Infarction	3 (4)	2 (8)	0.331
Hydrocephalus	1 (1)	4 (17)	0.01
Anti-TB medication[b]	16 (20)	24 (100)	<0.001
EVD insertion	0	4 (17)	0.002
Length of the hospital stay, median days (IQR)	9 (6-14)	26 (14-80, n=23)	<0.001
Outcome, n (%)			
In-hospital crude mortality	0	2 (8)	0.053
Neurologic sequelae at discharge	17 (22)	10 (46, n=22)	0.025
Post discharge 1 month	17 (22)	10 (46, n=22)	0.025
Post discharge 2 months	12 (15)	9 (41, n=22)	0.009
Post discharge 3 months	9 (11)	9 (41, n=22)	0.003

[a]Defined as receipt of immunosuppressive drugs such as steroids or immunosuppressant drugs within a previous month.
[b]Number of patients who received anti-TB therapy.
VZV, varicella-zoster virus; TB, tuberculosis; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; EVD, external ventricular drainage; IQR, interquartile range.

ingitis and 14 days (IQR, 6.5 -15.0; n=21; $P < 0.001$) in patients with TBM. CSF examination was performed within 24 hours in 91% (72/79) of patients with VZV meningitis and 86% (18/21) of patient with TBM ($P = 0.43$). Twenty six patients (33%) with VZV meningitis had cutaneous blisters; among the 26 patients with cutaneous blisters, 7 patients (27%) had ear vesicles.

TBM patients had more severe clinical presentations than patients with VZV meningitis (Table 1, 2). Altered mental status (71% [17/24]) and seizure (21% [5/24]) were more common in patients with TBM than those with VZV meningitis (15% [12/79]; P <0.001 and 3% [2/79]; $P = 0.007$, respectively). The number of encephalitis cases was significantly higher amongst TBM patients (67% [16/24]) than in VZV meningitis patients (19% [15/79]; P <0.001). During the course of treatment, intensive care unit (ICU) hospitalization was more common amongst TBM patients (42% [10/24]) than in VZV meningitis patients (10% [8/79] $P = 0.001$).

2. TBM-mimicking VZV meningitis

Of the 79 patients with VZV meningitis, 63 (80%) patients did not receive empirical anti-tuberculous treatment (Group 1). Sixteen (20%) patients received empirical anti-tuberculosis treatment (Group 2), the median duration of which was 10 weeks (interquartile range 1-45). The 24 patients with TBM were classified as Group 3. The demographic data and clinical manifestations of VZV meningitis (Group 1 *vs.* Group 2) and TBM (Group 3) are shown in Table 3. Altered mental status, ICU admission, neurologic sequelae, CSF protein levels, and CSF adenosine deaminase levels revealed a trend of being higher in Group 3 than Group 2, which was higher than Group 1. However, the CSF/serum glucose ratio was significantly lower in Group 3 than in Group 1 or Group 2.

Discussion

In this study, we found that about one fifth of patients with VZV meningitis presented with very similar clinical features and CSF profiles as those with TBM. As such, these patients with severe VZV meningitis received empirical anti-tuberculous treatment with a presumptive diagnosis of TBM in an intermediate TB burden country. Some clinical features proved helpful in differentiating between these two diseases, such as CSF/serum glucose ratio and vesicular skin eruption, which occurred in only one third of patients with VZV meningitis. Thus, we can infer from this study that clinical suspicion and appropriate microbiological work-up for VZV meningitis and TBM are warranted, especially in an intermediate or high-TB burden country.

The CSF profile of VZV meningitis is lymphocytic pleocytosis and relatively high CSF protein levels [3], which overlaps with those of TBM patients [8]. However, TBM is difficult to diagnose with certainty, especially in the early phase, because the laboratory tests are insensitive [9]. Conventional methods, such as the direct examination of CSF, are positive in only 5-20% of cases. The rate of positivity is about 40% in culture, which takes about 6 weeks [10, 11]. The results of PCR studies in the CSF have shown a 86-100% specificity but sensitivities ranging from 32-86% [12-16]. Clinical suspicion still plays a major role, and anti-tuberculous treatment and other agents, such as anti-bacterial and anti-viral agent, are frequently combined while awaiting culture and PCR reports, because the gap between the sensitivity of microbiologically-confirmed TBM and that of clinically-diagnosed TBM is large. The use of the PCR in the diagnosis of VZV meningitis is helping with excellent sensitivity and specificity [17, 18]. This assay can be

Table 2. Cerebrospinal fluid findings in patients with central nervous system infections caused by varicella-zoster virus and *Mycobacterium tuberculosis*

	VZV (n = 79)	TB (n = 24)	*P*-value
CSF findings			
WBC, cell/mm^3	210 (71 - 420)	213 (123 - 383)	0.93
Neutrophil, %	1 (0 - 6)	26 (11 - 61)	<0.001
Lymphocyte, %	80 (57 - 89)	60 (27 - 74)	0.002
Glucose, mg/dL	56 (51 - 64)	32 (18 - 44)	<0.001
CSF/serum glucose ratio	0.49 (0.44 - 0.53)	0.21 (0.15 - 0.33) (n = 22)	<0.001
Protein, mg/dl	99 (68 - 135)	202 (129 - 322)	<0.001
ADA, U/L	4.1 (1.8 - 6.8) (n = 76)	13.3 (9.2 - 20.8) (n = 21)	<0.001

Data are presented as median (IQR).
VZV, varicella-zoster virus; TB, tuberculosis; CSF, cerebrospinal fluid; WBC, white blood cell; ADA, adenosine deaminase; IQR, interquartile range.

Table 3. Comparison of clinical characteristics and laboratory findings between patients with central nervous system infections caused by varicella-zoster virus and *Mycobacterium tuberculosis*

	VZV without TB medication (Group 1, n = 63)	VZV with TB medication (Group 2, n = 16)	TB (Group 3, n = 24)	*P*-value		
				Group 1 *vs.* Group 2	Group 2 *vs.* Group 3	*P* for trend
Clinical manifestations, n (%)						
Cutaneous zoster	25 (40)	1 (6)	0	0.01	0.4	<0.001
Altered mental status	6 (10)	6 (38)	17 (71)	0.01	0.04	<0.001
Seizure	2 (3)	0	5 (21)	>0.99	0.07	0.009
Clinical diagnosis, n (%)				0.001	0.29	<0.001
Meningitis	56 (89)	8 (50)	8 (33)			
Encephalitis	7 (11)	8 (50)	16 (67)			
CSF findings						
WBC (cell/mm^3)	230 (65-500)	201 (93-419)	213 (123-383)	0.51	0.69	0.55
Neutrophil, %	1 (0-6)	2 (0-10)	26 (11-61)	0.56	<0.001	<0.001
Lymphocyte, %	79 (58-89)	83 (54-91)	60 (27-74)	0.61	0.17	0.03
Monocyte, %	14 (7-22)	10 (7-26)	10 (5-14)	0.82	0.37	0.02
Lymphomonocyte, %	97 (91-100)	96 (68-98)	74 (39-89)	0.73	0.001	<0.001
Glucose (mg/dL)	57 (52-64)	56 (46-68)	32 (18-44)	0.52	0.04	<0.001
CSF/serum glucose ratio	0.50 (0.45-0.53)	0.47 (0.36-0.51)	0.21 (0.15-0.33, n = 22)	0.07	0.001	<0.001
Protein (mg/dL)	85 (58-127)	128 (100-210)	202 (129-322)	0.001	0.2	<0.001
ADA (U/L)	3.4 (1.7-6.0, n = 60)	7.7 (4.8-13.0)	13.3 (9.2-20.8, n = 21)	<0.001	0.003	<0.001
Highest ADA (U/L)	3.6 (1.7-6.4, n = 60)	12.1 (8.0-15.0)	16.6 (11.7-31.6, n = 23)	<0.001	0.03	<0.001
Course of illness						
ICU hospitalization, n (%)	4 (6)	4 (25)	10 (42)	0.049	0.28	<0.001
Assisted ventilation	1 (2)	2 (13)	6 (25)	0.10	0.44	<0.001
Outcome, n (%)						
Neurologic sequelae at discharge	11 (18)	6 (38)	10 (46, n = 22)	0.09	0.62	0.007

Data are presented as median (IQR).
VZV, varicella-zoster virus; TB, tuberculosis; CSF, cerebrospinal fluid; WBC, white blood cell; ADA, adenosine deaminase; ICU, intensive care unit.

carried out rapidly, within a day or two. But the test cannot be easily performed in a resource-limited country, especially TB endemic area.

Our results showed that 16 patients (20%) with VZV meningitis received anti-TB medication in their drug regimen. Patients with severe VZV meningitis had serious clinical manifestations and an overlapping CSF profile with TBM patients, thus clinicians might frequently misdiagnose severe VZV meningitis as TBM. However, patients with severe VZV meningitis had significantly higher CSF/serum glucose ratio and glucose levels than those with TBM. Therefore, CSF profile could provide an important clue in an early stage differential diagnosis between severe VZV meningitis and TBM.

The adenosine deaminase (ADA) level in CSF has been proposed as a useful marker for diagnosing TBM [19]. Several studies have reported that when a cut-off value of 10 U/L was used, specificity was 85-97% [20-22]. However, among 16 patients with severe VZV meningitis, 10 (63%) patients had a CSF ADA level greater than 10 U/L. In addition, 4 (25%) patients had a CSF ADA level more than 15 U/L. In this context, the level of ADA in CSF overlapped between severe VZV meningitis patients and TBM patients. Therefore, CSF ADA, which is simple and inexpensive, should be used with caution for diagnosing TBM.

This study has several limitations. First, the retrospective nature of this study makes it difficult to analyze which factors affected the decision regarding empirical anti-tuberculous treatment in patients with severe VZV meningitis. The lack of systematic evaluation of skin lesions in the enrolled patients might underestimate the frequency of skin lesions in patients with VZV meningitis. Second, we cannot rule out co-infection of VZV meningitis and TBM with certainty, because the currently available tests are not sufficiently sensitive to rule out TBM, and some patients with VZV meningitis received empirical anti-TB treatment for several weeks. However, there are few cases reported of combined VZV and TBM. Third, empirical TB medication in patients who were suspicious of TBM was decided by the discretion of the attending physician. Because this study was conducted in an intermediate TB burden country, the threshold of empirical anti-TB treatment may be different in areas with different epidemiologies of TB. Hence, further prospective well-designed studies are needed to determine a differential diagnosis for patients with suspected VZV meningitis in other areas. Fourth, this study was performed in a single large tertiary referral center, disease spectrum was likely skewed toward the more severe end. Therefore there could be a patients' selection bias. Viral etiology of meningitis could differ according to place, Caution is needed to interpreting results of our single center-study in different conditions.

In conclusion, about one fifth of VZV meningitis cases presented as severe manifestations, mimicking mild forms of TBM. The CSF/serum glucose ratio might be useful to differentiate VZV meningitis from TBM until definite diagnostic tests are available. Physicians should keep in mind that a differential diagnosis between severe VZV meningitis and a mild form of TBM is needed.

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Conflicts of Interest

No conflicts of interest.

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