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Unravelling the intricacies of Coexistent HSV-1, EBV and Tubercular Meningoencephalitis Aimidist the Enigma of initial CSF fluid negativity for tubercular involvement –A case report

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Abstract

In the intricate realm of central nervous system infections, coexistent pathogens pose a formidable diagnostic challenge. We present a compelling case of a patient grappling with the simultaneous presence of Herpes Simplex Virus Type 1 (HSV-1), Epstein-Barr Virus (EBV), and Tubercular Meningoencephalitis. The clinical intrigue deepens as conventional cerebrospinal fluid (CSF) analysis, typically a diagnostic mainstay for tubercular involvement, remains stubbornly negative.

This case underscores the complexity of simultaneous viral and mycobacterial infections within the central nervous system, weaving a narrative of diagnostic ambiguity. Through an in-depth exploration of the patient's clinical course, imaging findings, and high index of clinical suspicion, we unravel the layers of this diagnostic enigma. The coexistence of HSV-1 and EBV further complicates the clinical presentation, demanding a nuanced approach to therapeutic intervention.

The focal point of our report lies in the challenges posed by the paradoxical absence of tubercular markers in the initial CSF in addition to rare coexistence of viral and tubercular infection in immune competent individuals.

This case report not only contributes to the expanding literature on coexistent viral and mycobacterial infections but also underscores the need for heightened clinical suspicion when faced with atypical presentations. The pursuit of diagnostic clarity in the face of such complexity serves as a reminder of the ongoing evolution required in the field of neuroinfectious diseases.

Keywords: CSF, EBV, HSV – 1.

Case Report

A 45-year-old female was admitted to our hospital with a six-day history of low-grade fever, accompanied by an evening rise in temperature, and projectile vomiting, with approximately 10 to 20 episodes. This was followed by irrelevant talking and decreased sensorium on admission, she was lethargic with a GCS of E1V1 M3 and the examination revealed normal vital signs. In the neurological examinations, she was drowsy and unresponsive to verbal commands. Her pupils were normal sized and reactive to light. Other examinations demonstrated rigidity in all four limbs along with positive meningeal signs.

On admission, the laboratory analysis revealed a leukocyte count of 14,000 (segmental neutrophil 90%,

lymphocyte 6%, and monocyte 2%), hemoglobin level of 11.7 g/dl, platelet count of 173,000/µl, serum potassium of 4.1 mEq/dl, sodium of 141 mEq/dl, total calcium of 8.5 mg/dl, urea of 37 mg/dl, creatinine of 0.8 mg/dl, and glucose of 132 mg/dl. Cerebrospinal fluid (CSF) examination demonstrated normal findings with zero cells, a protein level of 26, and a sugar level of 77; ADA measured 2.2, and CBNAAT yielded negative results. Gram stain, fungal stain, and acid-fast bacilli (AFB) stain all returned negative results.

Triple serology results were also negative. In response to positive meningeal signs, the patient received empirical intravenous antibiotics and acyclovir.

Given the ostensibly normal CSF findings, a subsequent MRI of the patient's brain was conducted, revealing bilateral temporal lobe hyperintensities as demonstrated in image below.

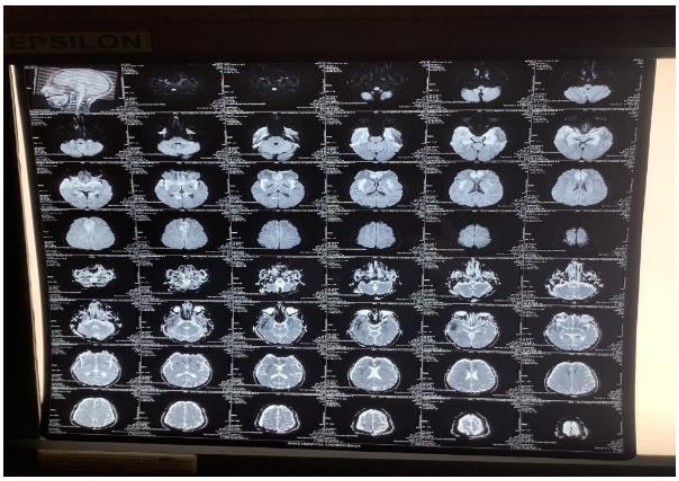

Figure 1

These details collectively contribute to the comprehensive clinical profile of the patient and warrant further investigation into the underlying etiology of the observed neurological manifestations. Cerebrospinal fluid (CSF) analysis for the viral panel definitively diagnosed the presence of HSV-1 and EBV encephalitis. Serological testing, however, did not align with the patterns indicative of autoimmune encephalitis. With viral encephalitis conclusively established through both radiological and laboratory examinations, the patient's treatment regimen was maintained with Acyclovir at a dosage of 500mg thrice daily.

Concurrently, the administration of other antibiotics was discontinued due to the absence of supportive evidence in the CSF for the involvement of alternative pathogens.

The complexity of this case heightened when, despite a 10-day course of Acyclovir and positive evidence of viral encephalitis in the cerebrospinal fluid (CSF), the patient exhibited minimal improvement in measurable parameters.

Considering the patient's origin from a tribal, hilly area recognized for tuberculosis endemicity, tuberculosis was reconsidered as a potential etiology, even in the absence of initial CSF evidence. To investigate tuberculosis, a contrast-enhanced computed tomography (CECT) scan of the chest, abdomen, and pelvis was conducted. The results revealed fibro consolidation patches in the apical segments of the right upper lobe and apicoposterior segment of the left upper lobe, accompanied by associated traction bronchiectasis in the left upper lobe. A tree-in-bud pattern was observed in centrilobular nodules, along with a few hyperdense mediastinal nodes as demonstrated in image below.

Figure 2

Given the patient's history from an endemic area and suggestive radiological evidence of a possible tubercular etiology, coupled with the lack of improvement on Acyclovir, tuberculosis was considered as the next plausible etiology. Subsequent CSF analysis revealed white blood cells at 30/mm³ (lymphocyte 80%, neutrophil 20%), red blood cells at 50/mm³, protein at 168 mg/dl, and sugar at 45 mg/dl. Armed with this compelling evidence, the patient was initiated on anti-tubercular therapy (ATT) in addition to Acyclovir.

Ten days post-commencement of ATT, the patient exhibited a favorable response, marked by significant improvement in sensorium and an enhancement in Glasgow Coma Scale (GCS) from E1V1M3 to E4V4M5.

This shift in therapeutic strategy underscores the paramount importance of a meticulous diagnostic approach, particularly in regions endemic for tuberculosis, to optimize patient outcomes.

Discussion

Tuberculosis is among the oldest documented and historically most lethal infectious diseases of humans and remains a serious world public health problem. Tuberculosis meningitis (TBM) is the most severe form of tuberculosis, with a high mortality rate and risk of neurological involvement.

The global burden of TBM is far underestimated because of the difficulties in making a correct diagnosis [1]. The traditional “gold standard” diagnostic test for TBM involves growing the pathogen Mycobacterium tuberculosis in culture, a process that is insensitive and time-consuming, thus often resulting in delayed diagnosis and treatment. The main reasons for a false-negative result of M. tuberculosis culture are low abundance of the pathogen in cerebrospinal fluid (CSF), and the need for a high standard of laboratory equipment and procedures [2]. As an alternative to the traditional Ziehl–Neelsen smear (ZN smear), emerging Gene-xpert/RIF (Xpert) and metagenomic next-generation sequencing(mNGS) methods are more sensitive and faster, but the negative results still cannot exclude the diagnosis of TBM. Furthermore, the volume, preservation, processing, and antibiotic treatment of CSF can affect test results [3]. Therefore, in geographic regions with a high burden of TBM, especially in countries with limited laboratory access, the diagnosis of TBM often depends on clinical features and the treatment decisions are made empirically, based on an integrated assessment rather than objective evidence of the pathogen.

Timely and accurate initiation of empirical anti-tuberculosis treatment can

significantly improve mortality and prognosis. Diagnostic guidelines of TBM proposed by the British Infection Society [4], Indian [5], Chinese medical association [6], and the American Thoracic Society [7] indicate that all patients suspected of TBM should start empirical anti-tuberculosis treatment immediately with a four-drug regimen, without waiting for microbiological or molecular diagnostic confirmation. However, no unified clinical diagnostic standard is so far available, and the available scoring systems that are widely used in the clinical setting are notoriously insensitive and nonspecific.

EBV is a well-known pathogen for infectious mononucleosis (IM). EBV infections have various manifestations alone or accompanied by clinical features of IM, such as meningoencephalitis, encephalitis, seizure, peripheral neuritis, Guillain Barre Syndrome, Bell’s palsy, and cerebellar ataxia(8,9,10).

EBV infections of the CNS can occur in the absence of IM (11).This finding finds consistency with that of our case as she was having no concomitant infectious mononucleosis.

The most common cause of sporadic encephalitis is due viral infection with herpes simplex type 1 (HSV1). It is characterized usually by the acute onset of fever, headache, seizures, focal neurologic signs, and impaired consciousness [12]. Herpes simplex viral encephalitis (HSVE), if not treated, is associated with a high mortality rate of up to 70% within 7-14 days and high morbidity of up to 90% (mostly neurological sequelae) among the survivors therefore making its early and accurate diagnosis of critical importance [12–15]. Prompt and early treatment with Acyclovir has been shown to decrease the mortality to approximately 20% [13,16].

The combination of a clinical history, a suggestive CT scan or MRI of the brain and the examination of the CSF by microscopy, biochemical analysis and DNA PCR for the presence of HSV DNA is needed for diagnosis of HSVE. The DNA PCR for HSV of the CSF is considered the gold standard test with sensitivity of 94-98% and specificity of 98-100% [17]. These studies perfectly correlate with the findings with our case as our initial suspicion of the patient having viral encephalitis was based on findings on MRI and thereafter correlated by CSF fluid positivity for HSV 1.

The coexistence of all the three infections in an immune competent individual with initial CSF fluid negativity for tuberculosis is a diagnostic dilemma that surrounded this case and has previously not been documented in literature. However the probable mechanism of coexistence of viral and tubercular infections finds a mention in a study by Tae Gun Kang etal entitled “Viral coinfection promotes tuberculosis immunopathogenesis by type I IFN signaling-dependent impediment of Th1 cell pulmonary influx”(18). Viral coinfection significantly suppresses Mtb-specific IFN-γ production, with elevated bacterial loads and hyperinflammation in the lungs. Type I IFN signaling blockade rescues the Mtb-specific IFN-γ response and ameliorates lung immunopathology. (18),although the said article broadly highlights the immunopathology with respect to the lung but the same may serve a possible explanation for such coinfection in the brain as well .

Conclusion: While individual instances of meningoencephalitis caused by Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), and Tuberculosis have been extensively documented in the literature, the concurrent infection involving all three organisms represents a rare and intricate presentation. The diagnostic challenge is further heightened by the initial cerebrospinal fluid (CSF) negativity for tubercular markers, underscoring the need for clinicians to uphold a vigilant and astute approach in the evaluation of meningoencephalitis cases.

This exceptional case serves as a reminder of the potential diagnostic complexity that may arise when multiple infectious agents are involved, especially when confronted with the elusive nature of tubercular infections in the CNS. The rarity of such coexistent infections emphasizes the necessity for healthcare practitioners to maintain a heightened clinical suspicion, enabling them to navigate the diagnostic intricacies efficiently.

As we continue to encounter diverse manifestations of neuroinfectious diseases, this report contributes to the broader understanding of the challenges associated with the simultaneous involvement of EBV, HSV, and Tuberculosis in meningoencephalitis. The implications of this rare presentation extend beyond the uniqueness of the case itself, highlighting the importance of a comprehensive and nuanced diagnostic approach to optimize patient care and outcomes. Future research and clinical experiences will undoubtedly further refine our

understanding of such complex presentations in the realm of neuroinfectious diseases.

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