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Clinical Reasoning: A Teenager With Chronic Meningitis—Does Occam's Razor Apply?

Author(s):
Harini Pavuluri, MD; DM[1]; Vysakha KV, MD; DM[1]; Bejoy Thomas, MD[2]; George C Vilanilam, MS; MCh[3]; Prakash Nair, MS; MCh[3]; Deepti A Narasimhaiah, MD[4]; Rajalakshmi Poyuran, MD[4]; Ramshekhar N Menon, MD; DM[1]

Corresponding Author:
Ramshekhar N Menon, rsnmenon@yahoo.com

Affiliation Information for All Authors: 1. Dept of Neurology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India; 2. Dept of Imaging Sciences & Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India; 3. Dept of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India; 4. Dept of Pathology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India

Equal Author Contribution:

Contributions:
Harini Pavuluri: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Vysakha KV: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Bejoy Thomas: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design
George C Vilanilam: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Prakash Nair: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Deepti A Narasimhaiah: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Rajalakshmi Poyuran: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Ramshekhar N Menon: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

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Abstract

A 14-year-old girl presented with subacute onset headache, fever, and vomiting and was managed initially with antibiotics for suspected bacterial meningitis. Her symptoms further evolved over the next few weeks with systemic signs and symptoms favoring chronic meningitis with raised intracranial pressure. After the etiological workup was unrevealing, she was started on empirical anti-tuberculous therapy. Following a period of partial improvement, symptoms recurred with a new-onset focal seizure. Her imaging findings evolved from features suggestive of focal leptomeningitis to multifocal heterogeneous enhancing cortical and subcortical lesions with hemorrhagic foci, leading to brain biopsy that confirmed diagnosis. Our case highlights the utility of diagnostic biopsy in patients with "chronic meningitis" in uncertain cases rather than confining the approach to the law of parsimony. The decision to initiate empirical therapy in chronic meningitis should be considered on a case-by-case basis and take into account factors such as clinical examination findings, immune status, recent exposures, and potential risks of treatment. Atypical MRI features should lower the threshold for meningo-cortical biopsy when indicated.

SECTION 1:

CASE VIGNETTE:

A 14-year-old girl presented with subacute onset, moderate intensity, progressive holocranial headache with photophonophobia, neck pain, recurrent episodes of vomiting, followed by low-grade fever and myalgias four days later. Ten days into the illness she was admitted to a local hospital after she did not improve following analgesics and antipyretics. She then underwent MRI which showed patchy, linear, and subtle leptomeningeal enhancement suggestive of meningitis (**Figure, A**) and CSF analysis which showed hypoglycorrhachia, elevated protein and lymphocytic pleocytosis. She was managed with empirical ceftriaxone and vancomycin for 10 days for presumed bacterial meningitis. She subsequently developed intermittent binocular horizontal diplopia with recurrence of intermittent headache and fever. She was referred to our center 45 days into the illness. On admission, her general

examination was unremarkable. Neurological examination showed right abducens palsy and positive Kernig and Brudzinski signs, with no other deficits. Following a repeat MRI brain **(Figure, B–C)**, lumbar puncture and extensive investigations, she was started on anti-tuberculous therapy (ATT) with steroids. There was marked improvement initially, however on attempted steroid taper after 4 months, she suffered recurrence of headache and one episode of focal-onset seizure with impaired awareness. Repeat examination did not reveal any features of raised intracranial pressure (ICP) or focal neurological deficits. MRI following clinical relapse showed multiple heterogeneous T2/FLAIR hyperintense cortical and subcortical lesions with multiple microhemorrhages on susceptibility-weighted imaging and patchy enhancement (**Figure, D–F)**, without diffusion restriction and normal MR spectroscopy and perfusion.

Question 1:What is the clinical approach to this patient with headache, and what etiological possibilities should be considered?

SECTION 2:

This patient presented with fever and subacute progressive headache with associated vomiting, photophonophobia and neck pain. Given the potential origin of pain from the meninges, proximal arteries of the circle of Willis, meningeal arteries or dural venous sinuses,[1,2] potential etiologies included pachymeningitis (from infectious causes or inflammatory etiologies including sarcoidosis, IgG4-mediated disease, and neoplastic processes), primary or secondary CNS angiitis and cerebral venous thrombosis with or without intracranial hypertension. While primary headache disorders like migraine, trigeminal autonomic cephalalgias are also possibilities, her progressive course and abnormal CSF profile made these conditions less likely. Secondary headache was suspected in view of neck pain, rigidity, recurrent vomiting, diplopia with fever, and myalgias. [2,3] Later in the disease course, development of focal-onset seizures may also indicate an evolving encephalitis or space-occupying lesion of probable infectious (bacterial, fungal, tubercular, cysticercosis), inflammatory (sarcoidosis, Behcet's disease, Wegener's granulomatosis or non-granulomatous connective tissues disorders with angiitis such as SLE, polyarteritis nodosa, Vogt Koyanagi Harada, primary CNS angiitis), or neoplastic etiologies (leukemia or lymphoma, given the patient's age).[4]

Question 2: What are the investigative approaches?

SECTION 3:

Imaging and cerebrospinal fluid (CSF) analysis are two seminal diagnostic modalities that should be considered in any patient presenting with a new onset secondary headache with or without fever, which often guide further diagnostic workup. Brain imaging should be undertaken prior to lumbar puncture in cases of headache/raised ICP to reduce the risk of herniation. Serial CSF analysis **(Table 1)** from time of symptom onset showed a persistent lymphocytic pleocytosis with hypoglycorrhachia and elevated protein. Other investigations and serial MRI findings are summarized respectively in **Table 1** and the **Figure**. The CSF findings of elevated protein and low glucose with pleocytosis which persisted for more than 6-8 weeks raised concern for chronic meningitis. The differential diagnosis is discussed in **Table 2**.[4,5]

Question 3: How do you interpret the imaging findings in this patient?

SECTION 4:

Infections usually produce a thin, linear enhancement **(Figure, A)** except for fungal meningitis and tuberculosis which cause thick, lumpy and nodular enhancement patterns. In addition, enhancement due to a neoplastic process is usually thick, lumpy and nodular; however, carcinomatous meningitis and haematological malignancies like lymphoma and leukemia can produce a thin linear enhancement pattern when compared to the solid tumours.[7] Presence of a cortical gyriform FLAIR hyperintensity with enhancement (**Figure, B–C**) was suggestive of a cortical laminar necrosis, either following a vascular insult or focal encephalitis[7]. These important vascular conditions include subacute infarcts, posterior reversible encephalopathy syndrome, and post-ictal vasodilatation. Inflammatory causes can include either infectious (e.g., HSV encephalitis) or non-infectious autoimmune disorders, with neoplasms being rare mimics[7]. MRI following clinical relapse **(Figure, D–F)** suggested a vasculitic process or systemic neoplasm, such as Hodgkin or non-Hodgkin's lymphoma (NHL).[8]

Question 4: What differential should be considered in the light of the clinical and investigative (imaging, CSF) findings, and how do you proceed further?

SECTION 5:

Progressive worsening of clinical and radiographic findings with persistent CSF abnormalities despite a 4-drug ATT regimen and steroid coverage prompted further etiological exploration. The final possibilities that should be considered include:

1. Infectious meningitis with secondary CNS vasculitis: Presence of fever at symptom onset and hypoglycorrhachia with lymphocytic pleocytosis raised concern for infection (fungal, tubercular, parasitic). However molecular diagnostics were negative for most infections and this patient was young and immunocompetent without prior history or exposure to tuberculosis. While immune reconstitution inflammatory syndrome[9] is still possible, atypical imaging features with microhemorrhages were less suggestive. Digital subtraction angiography (DSA) for vasculitis was also unremarkable.

2. Multicentric high grade glioma or CNS lymphoma: Normal perfusion and spectroscopy make glioma less likely. While CNS lymphoma is a strong possibility, atypical imaging features included extensive microhemorrhages, heterogeneous enhancement, peripheral location, and absence of diffusion restriction. Use of corticosteroids may also have mitigated these imaging findings.

As most investigations had been unrevealing, she underwent a neuronavigation-guided biopsy 6 months into the illness of an enhancing lesion in the right temporal lobe. Twenty-four hours after the biopsy, she required a decompressive craniectomy with uncinectomy and right temporal lobectomy after she developed encephalopathy with features of intracranial hypertension and CT demonstration of midline shift. Biopsy was suggestive of anaplastic large cell lymphoma (ALCL), a rare T-cell NHL variant **(Figure, G and H)**.

A whole body 18F-fluoro-deoxy-glucose positron emission tomography done subsequently showed multiple foci of hypermetabolism in muscles and body of the pancreas. She received 7 cycles of chemotherapy with high dose methotrexate, vincristine, procarbazine and dexamethasone and whole brain irradiation at a dose of 45 Gray in 25 fractions with excellent

response and achieved complete remission. Repeat PET and MRI showed no residual lesion or recurrence. No neurological or cognitive deficits were apparent on her last clinical evaluation.

Discussion :

Primary and secondary central nervous system lymphomas are a rare subset of NHL especially in the pediatric age group[10,11]. Primary CNS lymphoma is confined to the CNS parenchyma, meninges, cranial nerves, spinal cord, or intraocular compartment, while secondary CNS lymphoma results from systemic NHL that has disseminated to the CNS with a predilection for the dura and leptomeninges[12]. ALCL is a rare T-cell NHL which frequently involves lymph nodes and extra nodal sites like the bone marrow, liver, or gastrointestinal tract and rarely involves the CNS. Less than 50 cases of CNS ALCL have been reported[13]. ALCL has predilection for young adults (median age of onset 21 years) and is divided into anaplastic lymphoma kinase (ALK) positive and negative subtypes based on ALK expression. Our patient had systemic ALCL with cerebral involvement and ALK positive status (cytoplasmic and membrane).

Most cases present with meningeal involvement, suggestive of a dural origin of the tumor and can be misdiagnosed initially as chronic infectious of inflammatory meningitis, stemming from a fungal infection, tuberculosis, or sarcoidosis[13]. In a recent systematic review of 36 cases, one third of patients received initial empirical treatment with antibiotics, anti-tuberculous, and antiviral medications akin to our case[13]. Multiple lesions with meningeal involvement on imaging are common, however the presence of extensive microhemorrhages with perilesional edema are unique to our case. Diagnostic biopsy followed by methotrexate-based chemotherapy with or without radiotherapy is the recommended line of management. Younger age at onset, ALK positive status and methotrexate-based chemotherapy are favorable prognostic factors[13], also highlighted in our case.

This report underscores the clinic-radiological and pathological heterogeneity of ALCL with potential therapeutic and prognostic implications in a teenager suspected to have an infectious etiology for her chronic meningitis. The utility of diagnostic biopsy in patients with “chronic meningitis” is also emphasized in uncertain cases, rather than remaining confined to the concept of Occam’s razor (law of parsimony). This approach is error-prone as the principle

encourages us not to seek multiple diagnostic possibilities beyond what is most likely following clinical exam, imaging, and CSF analysis.[14] The decision to initiate empirical therapy with antibiotics or ATT and steroids (often driven by epidemiological considerations) in chronic meningitis should be considered on a case-by-case basis. This approach should also take into account the overall picture as well as potential risks of treatment that can lead to diagnostic delays and clinical deterioration. Use of empirical steroids can cause transient improvement, but can decisively alter the clinical, CSF, radiological and histopathological findings in cases of CNS lymphoma as highlighted in our report. In such situations a lower threshold for biopsy is warranted.

Figure - Serial MRI and final histopathology images

A. Subtle leptomeningeal enhancement noted 3 weeks into illness; B. FLAIR hyperintensity in the right parietotemporal lobe; C. Patchy enhancement of the hyperintense region on T1W contrast sequence noted at 6 weeks suggestive of progression; D. Multiple heterogeneous T2/FLAIR hyperintense cortical and subcortical lesions at the grey-white matter junction of the right fronto-temporal, parieto-occipital and left temporal lobe; E. Multiple foci of blooming on SWI and heterogeneous enhancement of the hyperintense lesions, F. Leptomeningeal enhancement on T1W contrast at 6 months; G. Histopathology images showing atypical large lymphoid cells with vesicular nuclei and prominent nucleoli and brisk mitotic activity on haematoxylin and eosin staining; H. CD30 positive atypical lymphoid cells on immunoperoxidase staining (Magnification = scale bar G,H: 50µm)

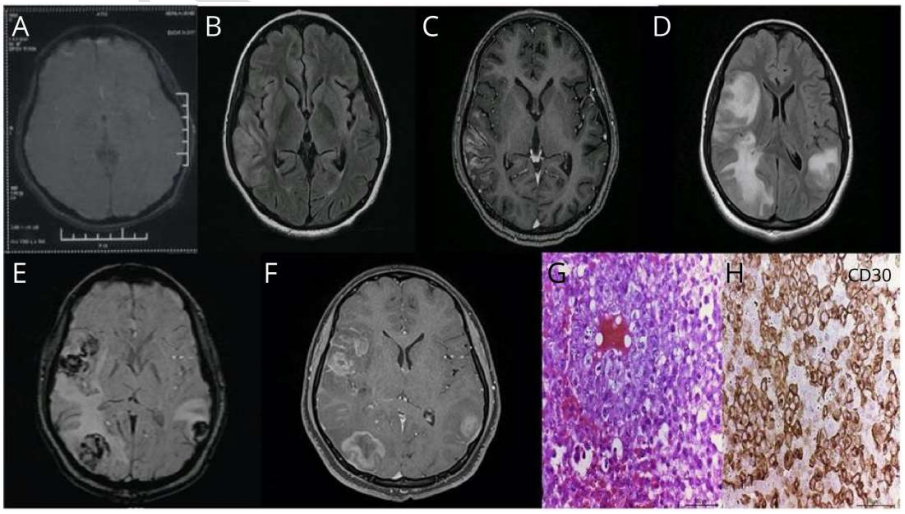

Table 1: Summary of serial CSF findings and other ancillary investigations

Serial CSF Analysis findings:					
Lumbar Puncture (Date)	I (26.10.17)	II (30.10.17)	III (20.11.17)	IV (05.12.17)	V (19.04.2018)
Total cell count (cells/cu mm)	**120**	**120**	**98**	**35**	**20**
Differential cell count (N- neutrophils; L-lymphocytes in %)	N 2, L 98; no dysplastic cells	N 8, L 92; no dysplastic cells	N 20, L 80	N 2, L 98	N 20, L 80
Malignant cell cytology	negative	negative	negative	negative	negative
Glucose (corresponding blood glucose; units: mg/dl)	**31 (170)**	**49 (182)**	**28 (120)**	**46 (117)**	**46 (95)**
Protein (unit: mg/dl)	**131**	**164**	**215**	**84**	**114**
Culture (bacterial, fungal and viral)	negative	negative	negative	negative	negative
PCR Meningitis/encephalitis panel				negative	negative
Cryptococcal antigen and pan fungal assay				negative	negative
Gene Xpert for mycobacterium				negative	negative
OTHER INVESTIGATIONS Hemogram, liver function tests, renal function tests, thyroid function tests- normal CRP, ESR, Procalcitonin- normal Vasculitis profile (ANA, anti-ds DNA, ANCA, APLA) and ANA profile- negative Brucella serology- negative Viral markers (HIV, HBsAg, anti HCV)- negative Serum Tumour markers- negative Serum calcium profile and ACE level- normal CT chest and abdomen contrast enhanced, DSA- normal					

Table 2: Differential diagnosis for chronic meningitis with significant hypoglycorrhachia and lymphocyte-dominant pleocytosis

The differentials to be considered in the setting of a CSF picture of chronic meningitis with significant hypoglycorrhachia and lymphocyte dominant pleocytosis[4-6]

Infective causes	**Non-infectious inflammatory causes**	**Neoplastic**
<u>Bacterial</u> • Partially treated bacterial meningitis • Mycobacterium tuberculosis and atypical Mycobacterial infections • Borreliosis • Nocardiosis • Brucellosis • Melioidosis • Syphilis <u>Fungal</u> • Cryptococcosis • Histoplasmosis • Coccidioides • Candidiasis • Aspergillosis • Phaeohyphomycosis <u>Parasitic</u> • Acanthamoeba • Balamuthia • Toxoplasmosis • Cysticercosis <u>Viral</u> • HIV • Herpes simplex 1 & 2 • lymphocytic choriomeningitis virus	• Sarcoidosis • Neuro-Behcet's disease	• Leukemia • Lymphoma (late relapse after steroid taper) • Leptomeningeal metastasis

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