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

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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 etiologic workup was unrevealing, she was started on empirical antituberculous therapy. After 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 meningocortical biopsy when indicated.

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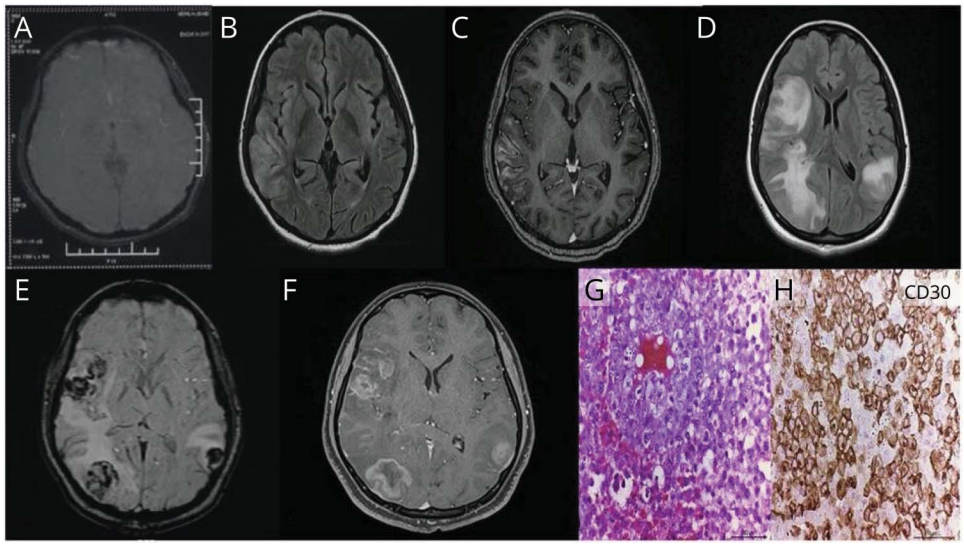
## Section 1

A 14-year-old girl presented with subacute onset, moderate intensity, progressive holocranial headache with photophonophobia, neck pain, and recurrent episodes of vomiting, followed by low-grade fever and myalgias 4 days later. Ten days into the illness she was admitted to a local hospital after she did not improve with 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. Neurologic examination showed right abducens palsy and positive Kernig and Brudzinski signs, with no other deficits. After a repeat MRI brain (Figure, B and C), lumbar puncture, and extensive investigations, she was started on antituberculous therapy (ATT) with steroids. There was marked improvement initially; however, on attempted steroid taper after 4 months, she suffered recurrence of headache and 1 episode of focal-onset seizure with impaired awareness. Repeat examination did not reveal any features of raised intracranial pressure (ICP) or focal neurologic deficits. MRI after clinical relapse showed multiple heterogeneous T2/fluid-attenuated inversion recovery (FLAIR) hyperintense cortical and subcortical lesions with multiple microhemorrhages on susceptibility-weighted imaging and patchy enhancement (Figure, D and F), without diffusion restriction and normal MR spectroscopy and perfusion.

### Question for Consideration:

1. What is the clinical approach to this patient with headache, and what etiologic possibilities should be considered?

**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 a 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 frontotemporal, 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 hematoxylin and eosin staining. (H) CD30-positive atypical lymphoid cells on immunoperoxidase staining (magnification = scale bar G, H: 50 μm). FLAIR = fluid-attenuated inversion recovery; T1W = T1-weighted; T2W = T2-weighted.

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## 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, immunoglobulin G4-mediated disease, and neoplastic processes), primary or secondary CNS angiitis, and cerebral venous thrombosis with or without intracranial hypertension. Although primary headache disorders, such as migraine and 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, or cysticercosis), inflammatory (sarcoidosis, Behcet disease, Wegener granulomatosis, or nongranulomatous connective tissues disorders with angiitis such as systemic lupus erythematosus, polyarteritis nodosa, Vogt Koyanagi Harada, or primary CNS angiitis), or neoplastic etiologies (leukemia or lymphoma, given the patient's age).[4]

### Question for Consideration:

1. What are the investigative approaches?

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## Section 3

Imaging and CSF analysis are 2 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 before 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 for Consideration:

1. How do you interpret the imaging findings in this patient?

**Table 1** Summary of Serial CSF Findings and Other Ancillary Investigations

| **Serial CSF analysis findings** | | | | | |
|---|---|---|---|---|---|
| **Lumbar puncture (date)** | I (October 26, 2017) | II (October 30, 2017) | III (November 20, 2017) | IV (December 5, 2017) | V (April 19, 2018) |
| **Total cell count (cells/mm$^3$)** | 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; mg/dL)** | 31 (170) | 49 (182) | 28 (120) | 46 (117) | 46 (95) |
| **Protein (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 tumor markers: negative
Serum calcium profile and ACE level: normal
CT chest and abdomen contrast enhanced, DSA: normal

Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; APLA = antiphospholipid antibody; CRP = C-reactive protein; DSA = digital subtraction angiography; ESR = erythrocyte sedimentation rate; HBSAg = hepatitis B surface antigen; HCV = hepatitis B virus.

**Table 2** Differential Diagnosis for Chronic Meningitis With Significant Hypoglycorrhachia and Lymphocyte-Dominant Pleocytosis

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

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

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## 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 hematological malignancies, such as lymphoma and leukemia, can produce a thin linear enhancement pattern when compared to solid tumors.[7] Presence of a cortical gyriform FLAIR hyperintensity with enhancement (Figure, B and C) was suggestive of a cortical laminar necrosis, either after a vascular insult or focal encephalitis.[7] These important vascular conditions include subacute infarcts, posterior reversible encephalopathy syndrome, and postictal vasodilatation. Inflammatory causes can include either infectious (e.g., herpes simplex virus encephalitis) or noninfectious autoimmune disorders, with neoplasms being rare mimics.[7] MRI after clinical relapse (Figure, D and F) suggested a vasculitic process or systemic neoplasm, such as Hodgkin or non-Hodgkin lymphoma (NHL).[8]

### Question for Consideration:

1. What differential should be considered in light of the clinical and investigative imaging and CSF findings, and how do you proceed further?

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## Section 5

Progressive worsening of clinical and radiographic findings with persistent CSF abnormalities, despite a 4-drug ATT regimen and steroid coverage, prompted further etiologic 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, and parasitic). However, molecular diagnostics were negative for most infections, and this patient was young and immunocompetent without history or exposure to tuberculosis. Although immune reconstitution inflammatory syndrome[9] is still possible, atypical imaging features with microhemorrhages were less suggestive. Digital subtraction angiography for vasculitis was also unremarkable.
2. Multicentric high-grade glioma or CNS lymphoma: normal perfusion and spectroscopy make glioma less likely. Although CNS lymphoma is a strong possibility, atypical imaging features included extensive microhemorrhages, heterogeneous enhancement, peripheral location, and absence of diffusion restriction. The 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 PET performed 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 neurologic or cognitive deficits were apparent on her last clinical evaluation.

## Discussion

Primary and secondary CNS 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 extranodal sites, such as 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 at onset 21 years) and is divided into anaplastic lymphoma kinase (ALK)–positive and ALK-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 causes 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, antituberculous, 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 is 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-radiologic and pathologic 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 because the principle encourages us not to seek multiple diagnostic possibilities beyond what is most likely after clinical examination, imaging, and CSF analysis.[14] The decision to initiate empirical therapy with antibiotics or ATT and steroids (often driven by epidemiologic considerations) in chronic meningitis should be considered on a case-by-case basis. This approach should also take into account the overall picture and potential risks of treatment that can lead to diagnostic delays and clinical deterioration. The use of empirical steroids can cause transient improvement but can decisively alter the clinical, CSF, radiologic, and histopathologic findings in cases of CNS lymphoma as highlighted in our report. In such situations, a lower threshold for biopsy is warranted.


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