A Case of Primary Autoimmune Meningitis with Hydrocephalus

Dear Editor,

Inflammatory cerebrospinal fluid (CSF) parameters persisting for more than a month without spontaneous resolution suggest chronic meningitis. The common etiologies are infections caused by bacteria, viruses, fungi, and parasites. A few cases have neoplastic etiology.[1] A specific cause may not be found in a few even after extensive evaluation. Autoimmune meningitis has been reported as part of autoimmune diseases such as systemic lupus erythematosus, Behcet's disease, sarcoidosis, and rheumatoid arthritis.[2-4] Hydrocephalus has been reported as a complication of several systemic autoimmune diseases.[5,6] There is one reported case of chronic autoimmune meningoencephalitis that responded well to immunotherapy in the literature.[7] However, hydrocephalus requiring ventriculoperitoneal shunting in a case of primary autoimmune meningitis has not been reported to date.

A patient in the thirties without any comorbidity was referred from a local hospital where the patient presented with high-grade fever, headache, blurring of vision, and vomiting of seven-day duration. A computed tomography (CT) scan of the brain with contrast performed in that hospital showed mild hydrocephalus with abnormal leptomeningeal enhancement, and the CSF revealed 60 cells/mm^3 (66% neutrophils and 33% lymphocytes) with glucose of 73 mg/dl (corresponding blood sugar of 122 mg/dl) and protein of 358 mg/dl. CSF adenosine deaminase level was 4.83 U/L (normal <10 U/L). Even after the initiation of ceftriaxone and acyclovir, the illness worsened and hence the patient was referred to our hospital. There were new symptoms such as nasal

twang of voice, deviation of angle of mouth to the right, and nasal regurgitation of food. On examination, the vitals were stable with a Glasgow Coma Scale (GCS) of E4V5M6. Examination of the cranial nerves revealed left lateral rectus palsy, left lower motor neuron facial palsy, bulbar palsy on the left, and neck stiffness.

Laboratory investigations showed elevated markers of inflammation (erythrocyte sedimentation rate (ESR)—44 mm/hr and C-reactive protein (CRP)—2.18 mg/L). Magnetic resonance imaging (MRI) of the brain with gadolinium (GAD) demonstrated mild hydrocephalus [Figure 1], and CSF on admission showed 100 cells/mm^3 (95% lymphocytes and 5% neutrophils) with glucose of 114 mg/dl (corresponding blood sugar of 210 mg/dl) and protein of 199 mg/dl [Table 1]. CSF smear and cultures were negative for bacteria, fungi and viruses. Cryptococcal antigen and GeneXpert for mycobacterium tuberculosis were also negative. Atypical cells were absent. A dilated ophthalmologic examination was normal. During the hospital stay, there was a drop in GCS, and a repeat CT showed an increase in hydrocephalus [Figure 2], and hence, ventriculoperitoneal shunting was carried out after ruling out other causes for GCS fall. A whole-body positron emission tomography (PET) CT performed to rule out carcinomatous meningitis was found to be normal.

The patient was empirically started on four-drug regimen of antituberculosis drugs namely isoniazid, rifampicin, pyrazinamide, and ethambutol along with steroid (dexamethasone) as there was a high suspicion of tuberculous meningitis and was discharged. Whenever the dose of steroid was tapered, the illness worsened, and then, the dose of steroid had to be increased. After 4 months of starting antitubercular treatment, a repeat CSF showed cells of 67/mm^3 (all lymphocytes), glucose of 72 mg/dl (corresponding blood sugar—130 mg/dl), and protein of 861 mg/dl [Table 1]. Infectious etiologies including tuberculosis (TB) were again negative. Clinical examination revealed signs of myasthenia in the form of proximal muscle fatiguability and a positive neostigmine test. Repetitive Nerve Stimulation test (RNS) and acetylcholine receptor (AChR) antibody in the serum were negative. A repeat AChR antibody was positive after one month. However, the CT chest did not reveal a thymoma. Autoimmune meningitis was suspected because of the poor response to antituberculosis treatment and because there was no confirmed infectious or neoplastic etiology. The other clues were associated myasthenia and worsening on tapering of steroids. Vasculitic workup, serum Glial Fibrillary Acidic Protein (GFAP), and Neuromyelitis optica spectrum disorder (NMOSD) turned out to

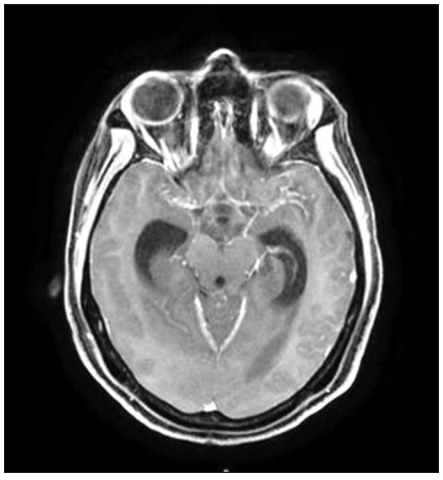

Figure 1: MRI of the brain with contrast showing hydrocephalus

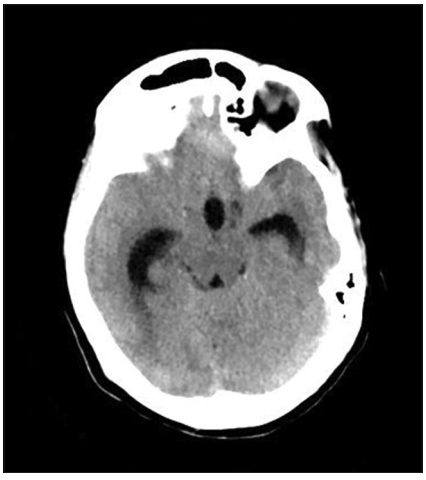

Figure 2: CT brain showing worsening hydrocephalus

Table 1: Trend of CSF study parameters observed during the course of treatment

CSF	Days of treatment												
	1[a]	4	29[b]	40	57	93[c]	103	110	120[d]	127[e]	258[f]	395	559[g]
Cells/mm^3 (Lymphocyte %)	100 (95)	12 (60)	665 (100)	157 (100)	120 (100)	225 (95)	155 (100)	7 (100)	67 (100)	35 (100)	22 (100)	12 (100)	7 (100)
Normal range (3–5 cells/mm^3)													
Glucose (mg/dl)	114	79	125	41	81	63	85	73	72	122	45	111	60
Corresponding blood sugar (mg/dl)	210	114	214	100	122	205	214	118	130	180	80	95	103
Protein (mg/dl)	199	24.5	65	61	68	2820	1777	63	861	80	680	435	306
Normal range (15–45 mg/dl)													

[a]The first CSF analysis that was performed at our institution, following this antituberculosis treatment was initiated, [b]CSF after the 1st steroid tapering attempt, [c]CSF after the 2nd steroid tapering attempt, [d]Intravenous methylprednisolone was started at 1 g/day after this CSF study, [e]CSF after intravenous steroid treatment, [f]Results of CSF study before initiation of IV cyclophosphamide, [g]CSF performed after completing 6 months of cyclophosphamide

be negative. Neuroimmunology workup for antibodies including paraneoplastic antibodies (antineuronal nuclear antibodies 1, 2, and 3, Purkinje cell cytoplasmic antibodies 1, 2, and Tr, amphiphysin antibody, collapsin response mediator protein 5 antibody, antiglial nuclear antibody 1 and Ma/Ta antibody, GAD 65, and N-methyl-D-aspartate (NMDA) receptor antibody) was negative. CSF autoimmune panel showed no named antibodies but showed unclassified neuronal antibodies to the nervous system.[8,9]

A trial of 5 days of pulse IV methylprednisolone at 1 g/day was given, which was continued once weekly thereafter and the symptoms completely subsided. Regular CSF monitoring was performed to ensure that the clinical response is accompanied by a CSF response [Table 1]. A repeat CSF after 3 months of immunotherapy showed a significant improvement (cells—22/mm^3 all lymphocytes, glucose—45 mg/dl (corresponding sugar—80 mg/dl), and protein—680 mg/dl). The patient improved symptomatically, and cranial nerve palsies subsided along with reduction in neck stiffness. The muscle power returned to normal. The patient was started on injection cyclophosphamide 750 mg/m^2 as a steroid-sparing agent, and six cycles were given over 6 months. Repeat CSF showed improvement with 7 cells/mm^3 (all lymphocytes), glucose of 60 mg/dl (corresponding sugar of 103 mg/dl), and protein of 306 mg/dl [Table 1]. Oral azathioprine 75mg per day was advised for maintenance immunosuppression. The patient was asymptomatic during the last OP visit after 31 months of regular follow-up and currently is on azathioprine 75 mg/day.

Our patient presented with clinical features of meningitis including raised intracranial pressure and hydrocephalus. CSF picture suggested a noninfectious cause. While on immunotherapy for autoimmune meningitis, the patient later developed features of myasthenia gravis. Hydrocephalus as a complication of systemic autoimmune diseases has been reported in literature.[5,6] However, primary autoimmune meningitis presenting with hydrocephalus requiring ventriculoperitoneal shunting has not been reported to date. Certain clinical clues strongly suggested an autoimmune etiology in our case: (1) inability to confirm a neoplastic or infectious etiology, (2) elevated markers of inflammation, (3) poor response to conventional treatment including antituberculosis treatment, (4) worsening of clinical and CSF parameters on steroid tapering, (5) elevated proteins in the CSF, (6) coexistent myasthenia, and (7) presence of unclassified neuronal antibodies in the CSF.

Autoimmune meningitis has varied presentations, and most of the time the tests for confirmation are inconclusive. Repeated clinical evaluations that patients often endure frustrates both the physician and the patient. They may also end up in more invasive investigations such as brain biopsies. Most of these cases are diagnosed as either tuberculous meningitis or idiopathic chronic meningitis.

Autoimmune meningitis requires a high degree of suspicion and should always be a differential diagnosis of chronic meningitis, especially when it is not responding to conventional therapies. Early determination and treatment can prevent morbidity and mortality in autoimmune meningitis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 17-Feb-2023 **Revised:** 25-Mar-2023 **Accepted:** 29-Mar-2023
Published: 11-Sep-2023

DOI: 10.4103/aian.aian_149_23