

Anti–Ma-1 and Anti–Ma-2 Antibodies in Isolated Fatal Hypothalamitis

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Lymphocytic hypothalamitis (LHT) is a rare disease characterized by pituitary dysfunction, autonomic instability, metabolic disturbances, and neuropsychiatric disorders. We report the case of a 30-year-old man found to have LHT that progressed despite treatment with methylprednisolone and intravenous immunoglobulin (IVIG). A literature review was conducted to identify prior studies pertaining to LHT. Our patient presented with several weeks of fatigue, cold intolerance, weight loss, confusion, and headache. Laboratory tests were consistent with panhypopituitarism. Brain magnetic resonance imaging revealed an infiltrative enhancing mass in the area of the hypothalamus, and stereotactic biopsy findings showed reactive inflammatory changes. A course of hormone replacement (levothyroxine), methylprednisolone, and IVIG was initiated. The patient's course was complicated by a fatal tonsillar herniation. Autopsy revealed LHT. The diagnosis and management of autoimmune LHT are challenging. The entity should be considered in the setting of panhypopituitarism with a hypothalamic mass. Differentiating paraneoplastic and nonparaneoplastic hypothalamitis should be established for management and prognosis. Definitive treatment remains unclear; treatment with corticosteroids should be attempted, followed by consideration of other immunosuppressive agents, such as rituximab. If a paraneoplastic syndrome is suspected, management should also be directed toward the primary tumor.

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Isolated lymphocytic hypothalamitis (LHT) is a rare disease, with only seven reported cases [1–7]. The condition is possibly an autoimmune disorder secondary to lymphocytic and plasma cell deposits in the hypothalamic area [1].

Diagnosis requires a high index of clinical suspicion, and early treatment is fundamental for the increased likelihood of a favorable prognosis. Based on the literature review, the condition can be diagnosed by biopsy, and first-line therapy would consist of corticosteroids.

Although the magnetic resonance imaging (MRI) characteristics of our case correspond with those seen in the literature, it remains questionable whether stereotactic biopsy (SB) is necessary before commencing treatment. In fact, in our case, the biopsy proved inadequate for conclusive diagnosis, and the disease progressed despite applying the standard regimen of corticosteroid therapy combined with intravenous immunoglobulin (IVIG). The presence of various onco-neural antibodies may provide clues to a paraneoplastic process; here we describe a presentation of LHT associated with anti–Ma-1 and anti–Ma-2 (Ta) antibodies. Also noteworthy was the discovery of hypermetabolic lymph nodes using positron emission

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; DI, diabetes insipidus; EVD, external ventricular drainage; HHV, human herpesvirus; IVIG, intravenous immunoglobulin; LHT, lymphocytic hypothalamitis; MRI, magnetic resonance imaging; PET, positron emission tomography; PLE, paraneoplastic limbic encephalitis; T1WI, T1-weighted imaging.

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tomography (PET)/computed tomography (CT). Postmortem evaluation failed to confirm the existence of underlying malignancy.

1. Case History

A 30-year-old male medical student presented with 3 weeks of fatigue, somnolence, chills, diaphoresis, decreased appetite, cold intolerance, 20-pound weight loss, and decreased libido. The patient's family attested to episodes of nausea, confusion, headache, visual hallucinations, confabulation, personality changes, and anterograde amnesia. An initial physical examination was unremarkable except for mild dehydration, dry skin, and generalized pallor; neuropsychiatric examination revealed only a disorientation to time.

Laboratory results proved consistent with panhypopituitarism (Supplemental Table 1). Other positive findings included an elevated cerebrospinal fluid (CSF) total protein of 166 mg/dL (15–45 mg/dL), an erythrocyte sedimentation rate of 20 mm/h (0–20 mm/h), and a ferritin of 1565 ng/mL (20–400 ng/mL). Results of lactate dehydrogenase, angiotensin-converting enzyme, β_2 macroglobulin, anti-Ro/SSA antibodies, anti-La/SSB antibodies, antinuclear antibodies, rheumatoid factor, c-reactive protein, HIV, *Mycobacterium tuberculosis* polymerase chain reaction, a hepatitis panel, blood cultures, and CSF studies (pressure, appearance, glucose, gram stain, white count, and cultures) were negative.

Serum anti-Ma-1 and anti-Ma-2 antibodies were positive, leading to the suspicion of a paraneoplastic limbic encephalitis (PLE).

An MRI of the brain with contrast revealed an infiltrative enhancing mass, $3.2 \times 2.8 \times 2.3$ cm in size, centered over the hypothalamus (Supplemental Fig. 1). The patient was initiated on levothyroxine 50 μ g and methylprednisolone 60 mg daily.

SB was performed, and results were consistent with reactive inflammatory changes (Supplemental Fig. 2). Serial follow-up computed tomography (CT) scans of the brain showed no signs of parenchymal or intraventricular bleeding.

An ultrasound of the testes was performed, showing a calcified lesion. This lesion was biopsied, showing a benign fibrous nodule, with atrophic seminiferous tubules and psammoma bodies. A CT scan of the chest, abdomen, and pelvis did not reveal further masses, nodules, or abnormalities.

A PET/CT scan revealed hypermetabolic activity within para-aortic and peri-iliac lymph nodes as well as in a subpleural nodule. These were unable to undergo biopsy due to a rapid deterioration of the patient's mental status.

After the SB, the patient's clinical course became complicated by the development of hypernatremia secondary to diabetes insipidus (DI). He was placed on desmopressin with an improvement in sodium levels.

A 48-hour trial of this regimen did not fully recover the patient's mental status. Methylprednisolone (1 g/d) and IVIG (0.4 mg/kg/d for 5 days) were started, with some neurologic improvement. The patient became alert and oriented to self, location, and time. However, the patient displayed a decreasing level of consciousness after 5 days of treatment. A repeat CT of the brain showed obstructive hydrocephalus induced by the mass effect of the severe hypothalamitis on the third ventricle. Neurosurgery was consulted to perform a bilateral external ventricular drainage (EVD).

Two days after the procedure, the patient became bradycardic and hypertensive, with a dilated left pupil found upon physical examination. He was rapidly intubated and administered mannitol. An emergent CT showed a large intraventricular hemorrhage and severe hydrocephalus that led to fatal tonsillar herniation.

The autopsy revealed LHT (Supplemental Fig. 3). The subpleural nodule, as well as the para-aortic and peri-iliac lymph nodes described from the prior PET/CT scan, were not found during this autopsy.

2. Discussion

Isolated LHT is an uncommon and mysterious disease. Symptoms are based on the brain structures affected [8, 9], and imaging may suggest a lesion compromising the hypothalamus.

The biopsy is considered a pillar for definitive diagnosis, yet it remains controversial whether such confirmation is needed to establish management.

LHT is believed to be an autoimmune condition [1]. It can be secondary to three distinct disease mechanisms. The first of these mechanisms involves LHT as a presentation of PLE [10]. The presence of a malignancy and its associated antigens triggers the development of antibodies against the cancer. Similar antigens are common among the central nervous system (CNS), leading to a paraneoplastic syndrome characterized by neuronal loss and inflammation in certain locations of the CNS (such as the hypothalamus). The syndrome usually precedes the detection of the tumor and of the antibodies and is often more debilitating than the malignancy [10]. The most commonly associated malignancies capable of bringing about PLE are small cell lung carcinoma, testicular teratoma, breast carcinoma, and Hodgkin's lymphoma [4, 8].

There are three types of antibodies that correspond with hypothalamic inflammation in the setting of PLE: anti-Ma-1, anti-Ma-2, and anti-Hu. Hu onconeural antigens are linked to small cell lung carcinoma [8, 9], whereas Ma-1 and Ma-2 are associated with testicular cancer [10, 11]. Positive serum levels of anti-Ma-1 and anti-Ma-2 antibodies in our patient raised the need for testicular ultrasound; imaging and biopsy revealed the absence of testicular malignancy. Nonetheless, the literature reports that, in cases with positive antibodies without an identifiable tumor, the tumor may be evading detection [8]. Additionally, the presence of anti-Ma-1 is associated with poor prognosis because these antibodies may target limbic structures, the brainstem, and the cerebellum [8, 11, 12]. Due to the detection of anti-Ma-1 and anti-Ma-2 antibodies in our patient, we cannot exclude the possibility that this isolated LHT is a localized presentation of PLE.

The second possible mechanism of LHT is characterized by a presentation of autoimmune lymphocytic hypophysitis, in which inflammation of the pituitary gland takes place and spreads to the hypothalamic area. In this disease process, there are no onconeural antibodies involved, ruling out the possibility of the LHT being secondary to a paraneoplastic syndrome. However, the presence of antipituitary antibodies has been documented. Imaging confirms pituitary gland inflammation that overextends and compromises the hypothalamus [5, 13]; empty Sella can be seen in late stages of the disease [5].

The third mechanism in which hypothalamitis may present involves other forms of autoimmune encephalitis with less clearly identified antigens, such as in the case of lupus cerebritis. In this third disease process, there are no identified antibodies as seen in the first two mechanisms discussed [14]. Antidesmopressin antibodies may be present in autoimmune hypothalamitis-associated DI; however, they are not specific and can also be found in idiopathic hypothalamic DI, histiocytosis, and craniopharyngioma [1].

The differential diagnosis includes infectious causes [e.g., herpes simplex virus, cytomegalovirus, human herpesvirus (HHV)6 and HHV7, West Nile Virus, Japanese encephalitis, tuberculosis, listeria, Lyme disease, toxoplasmosis, etc.] and a variety of other diseases (e.g., histiocytosis, sarcoidosis, metastatic disease, lymphoma, glioma, lupus cerebritis, acute disseminated encephalomyelitis, etc.) [1, 8, 14, 15].

MRI is the best diagnostic imaging modality for LHT [7]. In T1-weighted imaging (T1WI), hypothalamitis is characteristically hypo- and iso-intense compared with normal white matter. There is also a loss of bright signal intensity of neurohypophysis (as seen in our case) as well as mild hyperintensity of the hypothalamic lesion in T2-weighted imaging. Post-contrast T1WI shows heterogeneous and periphery-oriented enhancement of the lesion with a polygon-shaped straight flange (polygon sign) and optic chiasm edema [7]. These unique imaging features of hypothalamitis would facilitate in distinguishing the condition from nonnecrotic lymphoma (which would instead show postcontrast homogeneous enhancement on T1WI) [16], thereby preventing misdiagnosis. For this reason, MRI is a valuable tool in the differential diagnosis.

After imaging studies displaying these characteristic features, lumbar puncture along with CSF studies are the next expected step in the diagnostic process. Lumbar puncture and CSF studies in LHT can detect lymphocytic pleocytosis and elevated proteins that are likely indicative of a meningeal reaction to hypothalamic inflammation [8, 15]. Additionally, CSF

studies can assist in the differential diagnosis by identifying the presence of a lymphoma in the cytology [14]. In our case, serum and CSF antibodies were ordered; however, only serum anti-Ma-1 and anti-Ma-2 antibodies were detected.

Histopathology is considered the gold standard for the diagnosis of LHT [3, 6]. Although our patient's biopsy revealed infiltrates of lymphocytes, plasma cells, and histiocytes suggestive of an inflammatory process, the diagnosis of LHT could not be confirmed until autopsy. This case illustrates how SB findings may not be specific for a particular autoimmune etiology [14].

Although multiple surgical approaches for biopsy have been reported in the literature (including stereotactic, trans-sphenoidal, and intraventricular approach) [6, 17], careful consideration must be taken to lessen the risk of complications like edema, hematoma, syndrome of inappropriate antidiuretic hormone, or DI due to the hypothalamus' vasculature and location of its nuclei. It remains questionable as to whether the severe swelling of the hypothalamus in our patient's case originated secondarily to the progression of the disease or to biopsy-related trauma. In any case, we suggest that biopsy not be used for ruling out conditions that can be eliminated with less invasive techniques, such as in the case of infection or CNS lymphoma. A further complication to our patient's course occurred after performing the EVD. Although the EVD transiently relieved intracranial pressure, the trauma caused by the procedure led to intraventricular hemorrhage that further worsened the hydrocephalus, generating an ultimately fatal tonsillar herniation.

The following criteria are proposed as an alternative diagnostic approach without the need for biopsy:

1. Subacute onset (<3 months) of short-term memory loss, altered mental status or psychiatric symptoms [15], symptoms of panhypopituitarism, or hypothalamic involvement
2. Laboratories confirming panhypopituitarism
3. CSF showing pleocytosis, elevated proteins, or antibodies consistent with PLE [15]
4. MRI features suggestive of a lesion compromising the hypothalamus on postcontrast T1WI with heterogeneous and peripheral enhancement of the lesion with a polygon sign and optic chiasm edema [7]
5. Reasonable exclusion of other causes [15] through laboratory tests confirming negative results of angiotensin-converting enzyme, β_2 macroglobulin, double-stranded DNA, anti-Smith, antiphospholipid antibodies, anti-Ro/SSA antibodies, anti-La/SSB antibodies, antinuclear antibodies, rheumatoid factor, C3 and C4 levels, HIV, CSF cytology for malignancy (including lymphoma), herpes simplex virus/cytomegalovirus/varicella-zoster virus/enterovirus/HHV6/HHV7 (via polymerase chain reaction), Lyme/West Nile virus/syphilis/toxoplasmosis/tuberculosis (via serology), *Cryptococcus* (via latex agglutination antigen test), antigen enzyme-linked immunosorbent assay for *Aspergillus fumigatus*, listeria/*Streptococcus*/aspergillosis (via culture), and mucormycosis (via nasal culture) [14]

We suggest comprehensive auto-antibody testing, despite the poor specificity of some results [8, 10]. We recommend starting with anti-Hu, anti-Ma-1, and anti-Ma-2 because they are frequently involved in the disease process [8–12]. If malignancy is found or if the pretest probability of malignancy is high, the appropriate imaging should be performed to localize the primary tumor.

The mainstay of first-line therapy consists of methylprednisolone (1 g intravenously daily) with consideration of plasmapheresis and later IVIG in the adjuvant setting. Infection and CNS lymphoma should be ruled out, if possible, before treatment initiation.

Second-line treatment options include rituximab, cyclophosphamide [14], and azathioprine [3, 5, 6] as well as dual-therapy rituximab with cyclophosphamide. Rituximab as monotherapy may be considered second line due to its more favorable side effect profile; it should be considered mainly in critically ill patients or if a patient remains significantly impaired after first-line therapy.

If PLE is suspected, diagnosis and management of the primary tumor are fundamental [14].

3. Conclusion

The approach and treatment of LHT prove to be challenging. We report a case in which the final diagnosis could only be made upon autopsy and not by biopsy, which is the gold standard for histologic diagnosis. The origin of our patient's increased hypothalamic swelling remains unclear. Whether the symptoms occurred secondarily to trauma postbiopsy or as a result of disease progression, we suggest that biopsy may not be necessary for the diagnostic process. A less invasive workup can be performed to rule out infectious processes and CNS malignancies (including lymphoma) to initiate therapy.

Differentiating paraneoplastic and nonparaneoplastic hypothalamitis is important for management and prognosis. Diligent workup is recommended to identify possible primary tumors to provide appropriate oncological management.

Our case also highlights the presence of anti-Ma-1 and anti-Ma-2 antibodies in isolated LHT, suggesting a possible presentation of localized PLE without the confirmation of an underlying malignancy, making this case unique.

Although high-dose steroids were previously reported to be effective first-line therapy, our patient demonstrated treatment failure. Treatment should be initiated promptly when there is a high clinical index of suspicion. While the patient is undergoing empiric treatment, other etiologies of encephalitis should be evaluated.

Additional investigation is necessary to further elucidate the optimal strategies for management of this rare disease. Add-on therapies may include IVIG, plasmapheresis, azathioprine, cyclophosphamide, and rituximab. Exclusive use of rituximab may be considered in critically ill patients or if the patient's condition is severely compromised after first-line therapy.

Although cases of LHT are rare, the mortality rate is high. Treatment success depends greatly on early detection and prompt treatment of the autoimmune disorder as well as the apt identification and treatment of any underlying malignancy.

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