

Paraneoplastic Syndrome of Inappropriate Antidiuretic Hormone Mimicking Limbic Encephalitis

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Objective: To compare the features of paraneoplastic syndrome of inappropriate antidiuretic hormone with those of limbic encephalitis.

Design: Case study.

Setting: Academic medical center.

Patient: A 46-year-old woman with progressive memory impairment, hyponatremia, and seizures.

Interventions: Magnetic resonance imaging of the brain, fluoro-2-deoxyglucose positron emission tomography of the body, and immunohistochemical analysis of a resected tumor.

Results: Though the patient presented with clinical

features of classic limbic encephalitis, magnetic resonance imaging, electroencephalogram, and cerebrospinal fluid analysis findings were unremarkable. Her chronic hyponatremia was ultimately found to be due to ectopic secretion of antidiuretic hormone by a neuroendocrine tumor with Merkel cell carcinoma phenotype.

Conclusions: Patients presenting with memory impairment, seizures, and hyponatremia should undergo a thorough workup for occult malignancy. In addition to considering classic immune-mediated paraneoplastic limbic encephalitis, the ectopic secretion of antidiuretic hormone should be included in the differential diagnosis.

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LIMBIC ENCEPHALITIS (LE) should be considered in the differential diagnosis of any patient who develops subacute memory loss, psychiatric symptoms, and seizures.¹ Limbic encephalitis may occur through paraneoplastic or autoimmune mechanisms, leading to an inflammatory response against neuronal antigens in the medial temporal lobe and limbic structures.²

Among the conditions that can mimic LE, chronic hyponatremia should also be considered. Chronic hyponatremia is associated with encephalopathy, recurrent falls, attention deficits, and seizures.³⁻⁵ The syndrome of inappropriate antidiuretic hormone (SIADH) causes most cases of chronic hyponatremia. Common causes of SIADH include malignancy, pulmonary disorders, traumatic brain injury and other central nervous system disorders, and medications. The syndrome of inappropriate antidiuretic hormone has been reported in conjunction with many types of cancer, most frequently in association with small cell lung carcinoma.⁶⁻⁸

Because of the common linkage between LE, SIADH, and cancer, a thorough

workup for malignancy needs to be initiated in any patient with subacute memory impairment, seizures, and hyponatremia. We discuss the case of a patient with this type of presentation who was ultimately found to have SIADH due to ectopic antidiuretic hormone (ADH) production by a neuroendocrine tumor with a Merkel cell carcinoma (MCC) immunophenotype.

REPORT OF A CASE

A 46-year-old right-handed white woman with an unremarkable medical history presented with progressive memory loss for 9 months, along with generalized seizures for 4 months. She took no medications. During 2 admissions at a local hospital, she was found to have a serum sodium level as low as 110 mEq/L (to convert this to millimoles per liter, multiply by 1). Lumbar puncture and magnetic resonance imaging (MRI) of the brain did not reveal any evident infection, inflammation, ischemia, hemorrhage, or tumor. Levetiracetam was initiated for seizure prophylaxis. She was discharged home but was no longer able to work and had difficulty driving. She was

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Table 1. Serum, Urine, and CSF Findings

Measure	Result	Reference Range
Serum		
Sodium	118 mEq/L	135-145 mEq/L
Creatinine	0.6 mg/dL	0.5-1.5 mg/dL
White blood cell count	6300/ μ L	4500-11 000/ μ L
Hemoglobin	12.9 g/dL	14-18 g/dL
Hematocrit	35.2%	40%-52%
Platelet count	369 000/ μ L	130 000-450 000/ μ L
C-reactive protein	1.1 mg/L	<4.0 mg/L
Morning cortisol	14 μ g/dL	6-23 μ g/dL
Thyrotropin	1.14 mIU/mL	0.35-5.5 mIU/mL
Urine		
Sodium	129 mmol/L	
Creatinine	126.0 mg/dL	
Osmolality	779 mOsm/kg	
CSF		
Opening pressure	20 cm/H ₂ O	
Glucose	55 mg/dL	
Protein	42 mg/dL	15-40 mg/dL
Red blood cells	0/ μ L	0/ μ L
Nucleated cells	2/ μ L	<5/ μ L
Bacterial culture	Negative	
Herpes simplex virus PCR	Negative	
Oligoclonal bands	Negative	

Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain reaction. SI conversion factors: To convert cortisol to nanomoles per liter, multiply by 27.588; C-reactive protein to nanomoles per liter, multiply by 9.524; serum creatinine to micromoles per liter, multiply by 88.4; hematocrit to proportion of 1.0, multiply by 0.01; hemoglobin to grams per liter, multiply by 10; serum sodium to millimoles per liter, multiply by 1; and white blood cell count to $\times 10^9/L$, multiply by 0.001.

subsequently referred to our medical center for further evaluation and treatment.

On review of systems, she reported an 18-kg weight loss in the past year, hair thinning for the past 2 years, and no menstrual period for the past 6 months. On neurological examination, she was awake and oriented to place but had difficulty with dates. She could not recount any details of personal events over the previous several months. Her speech was fluent, and she could name, repeat, and follow complex commands. Calculation was intact. Her short-term recall was 1 of 3 objects at 3 minutes. Her reflexes were symmetric but diminished throughout. Her cranial nerve, motor, sensory, and coordination examinations were normal.

Initial laboratory test results were notable for a serum sodium level of 118 mEq/L and serum osmolality level of 244 mOsm/kg (to convert to millimoles per kilogram, multiply by 1), with elevated urine sodium and osmolality levels (**Table 1**). She appeared euvoletic, and thyroid study results and cortisol level were normal. These findings were consistent with a diagnosis of SIADH. Along with fluid restriction and ongoing anticonvulsant treatment, she was initially treated with 1 g of intravenous methylprednisolone daily for 5 days for presumed LE, with no improvement in her symptoms.

Results of cerebrospinal fluid analysis were unremarkable (**Table 1**). Standard awake and asleep electroencephalogram demonstrated mild generalized slowing, no epi-

leptiform discharges, and no pathological response to photic stimulation. Contrast-enhanced MRI of the brain was normal. Results of serum and cerebrospinal fluid examination for paraneoplastic antibodies associated with LE were negative (**Table 2**). Notably, she was found to have a modestly elevated anti-N-type calcium channel antibody titer, of unclear significance (see "Comment" section).

To further evaluate for malignancy, we obtained computed tomography scans of her chest, abdomen, and pelvis, as well as a full-body fluoro-2-deoxyglucose positron emission tomography study. The fluoro-2-deoxyglucose positron emission tomography scan demonstrated an area of focal uptake in the anterior right thigh (**Figure 1A**). Magnetic resonance imaging of the right inguinal region confirmed a heterogeneously enhancing mass, concerning for malignancy (**Figure 1B**).

On histological analysis of the openly resected mass, the tissue comprised sheets and clusters of intermediate-sized cells with a neuroendocrine-type nuclear chromatin pattern (**Figure 1C**). Results of immunohistochemical analysis were positive for CK20, pankeratin, synaptophysin, chromogranin, and neurofilament and negative for CK7, TTF1, S-100, and HMB45. Notably, the tumor stained positive with anti-ADH antibody, indicating ectopic ADH secretion (**Figure 2**).

The pathological appearance of the mass was consistent with a neuroendocrine tumor involving the lymph node, with an immunophenotype of MCC. Based on these findings, we believe she had a metastatic MCC. No primary tumor was found on extensive further investigation.

Following tumor resection, the patient underwent local radiation therapy followed by systemic chemotherapy with etoposide and carboplatin. Her seizures remitted and serum sodium level normalized over a 2-week period. Fluid restriction was discontinued on hospital discharge, followed by gradual improvement in her cognition over the next 3 months. She had no further seizures, and her anticonvulsant treatment was tapered and discontinued. At 6 months after hospital discharge, she had returned to living independently and working full-time. At 1 year following diagnosis, she remained in complete remission. She has very subtle residual deficits in attention and long-term memory.

COMMENT

Limbic encephalitis commonly manifests with subacute memory loss and seizures. The co-occurrence of LE and SIADH should raise concern for malignancy, especially small cell lung carcinoma. Appropriate screening includes computed tomography scan of the chest, abdomen, and pelvis. Should computed tomography scan be unrevealing, a whole-body fluoro-2-deoxyglucose positron emission tomography scan should be performed.^{9,10} Vaginal or testicular ultrasonography should also be performed to fully evaluate for a gonadal or germ cell tumor.¹¹

Antibodies known to be associated with paraneoplastic LE include anti-Hu,¹² anti-Ma2,¹³ anti-N-methyl-D-aspartate receptor,¹⁴ anti-collapsin response-mediator protein type 5,¹⁵ anti-amphiphysin,¹⁶ and anti-GABA_B receptor.¹⁷ Limbic encephalitis causes medial temporal

Table 2. Serum and CSF Paraneoplastic Panel Results^a

Antibody	Serum Result	Reference Titer	CSF Result	Reference Titer
ANNA-1 (anti-Hu)	Negative	<1:240	Negative	<1:2
ANNA-2 (anti-Ri)	Negative	<1:240	Negative	<1:2
ANNA-3	Negative	<1:240	Negative	<1:2
Anti-PCA1 (anti-Yo)	Negative	<1:240	Negative	<1:2
Anti-PCA2	Negative	<1:240	Negative	<1:2
Anti-PCA-Tr	Negative	<1:240	Negative	<1:2
Anti-CRMP5 (anti-CV2)	Negative	<1:240	Negative	<1:2
Anti-amphiphysin	Negative	<1:240	Negative	<1:2
Anti-AGNA-1	Negative	<1:2		
Anti-striational	Negative	<1:60		
Anti-NMDA receptor	Negative	<1:2		
	Serum Titer, nmol/L	Reference, nmol/L		
Anti-voltage-gated potassium channel	0.01	≤0.02		
Anti-P/Q-type calcium channel	0.04	<0.02		
Anti-N-type calcium channel	0.13	≤0.03		
Anti-acetylcholine receptor	0.00	≤0.02		

Abbreviations: AGNA, anti-glia/neuronal nuclear antibody type 1; ANNA, antineuronal nuclear autoantibody; CRMP-5, collapsin response-mediator protein type 5; CSF, cerebrospinal fluid; NMDA, *N*-methyl-D-aspartate; PCA, Purkinje cell cytoplasmic antibody.

^aOnly anti-N-type calcium channel antibodies were found at a modestly elevated titer of 0.13 nmol/L. Anti-P/Q-type calcium channel antibodies were found at a borderline titer of 0.04 nmol/L.

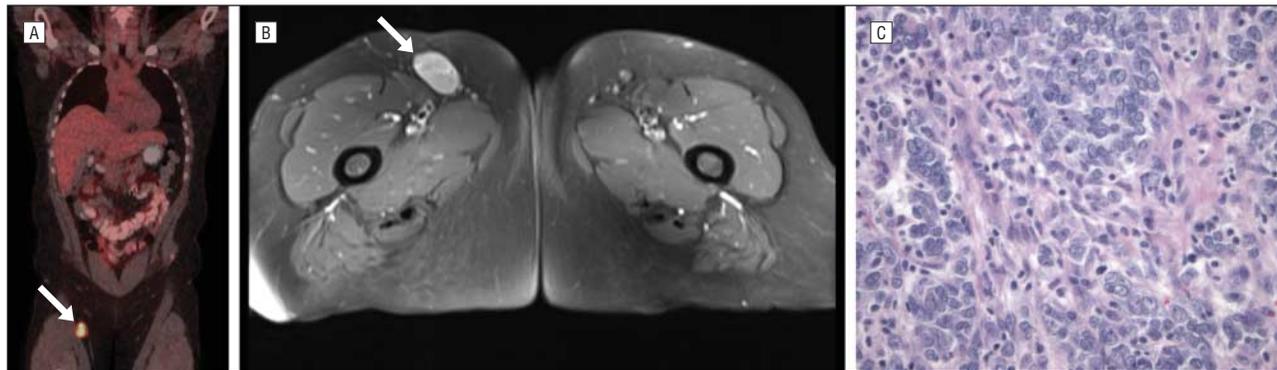


Figure 1. Radiological and pathological features of the neuroendocrine tumor with Merkel cell carcinoma phenotype. A, Whole-body fluoro-2-deoxyglucose positron emission tomography scan, demonstrating focal abnormal metabolic activity in the right thigh (arrow). B, T1-weighted magnetic resonance imaging of the thigh with contrast, demonstrating a heterogeneously enhancing subcutaneous mass (arrow). C, Hematoxylin-eosin stain of the resected tumor (original magnification $\times 10$).

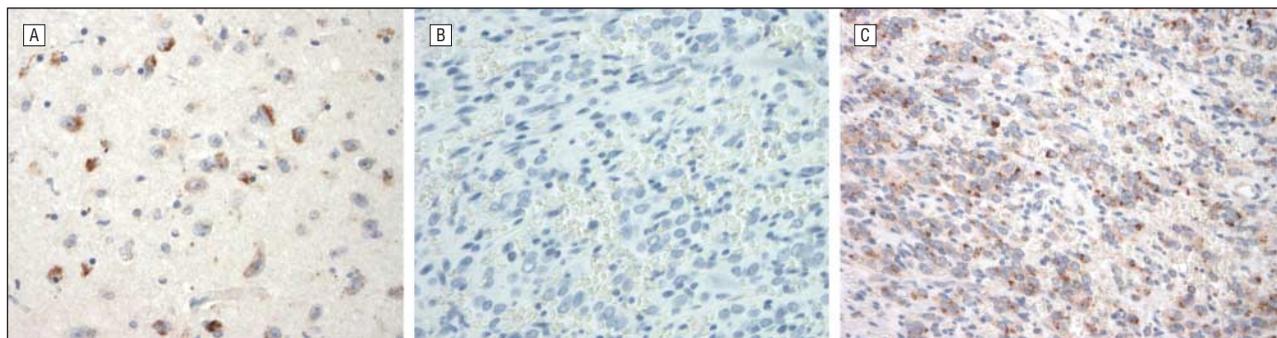


Figure 2. Ectopic antidiuretic hormone (ADH) secretion, immunohistochemical analysis with anti-ADH antibody (original magnification $\times 10$). A, Hypothalamic positive control tissue revealing positive cytoplasmic immunoreactivity in neurons. B, Resected tumor, negative control. C, Resected tumor, with positive cytoplasmic immunoreactivity for ADH in numerous tumor cells.

lobe hyperintensity on MRI in 70% to 80% of cases.¹ Other supporting findings for paraneoplastic LE include inflammatory changes in the cerebrospinal fluid and focal slowing or epileptiform activity on electroencephalogram.¹⁸ In patients without supporting MRI, cerebrospi-

nal fluid, and electroencephalogram findings, paraneoplastic LE is less likely, and alternative diagnoses should be strongly considered.

Paraneoplastic SIADH due to ectopic ADH production by neoplastic cells has been demonstrated in small

cell lung carcinoma¹⁹ and non-Hodgkin lymphoma.²⁰ Thus, the co-occurrence of paraneoplastic LE due to antitumor antibodies with SIADH due to ectopic ADH secretion by tumor cells may occur in rare cases.

Merkel cell carcinoma, or primary neuroendocrine carcinoma of the skin, is a rare and aggressive cutaneous tumor.²¹ In normal tissue, Merkel cells function as mechanoreceptors.²² They also function as neuroendocrine cells, secreting met-enkephalin, vasoactive intestinal polypeptide, substance P, and calcitonin gene-related peptide to transmit or transduce chemical information.²³ The histological appearance of MCC is similar to other neuroendocrine tumors, and immunohistochemical analysis is essential for diagnosis.²⁴

Treatment of MCC is based on excision of the tumor with wide margins and adjuvant radiation therapy.²⁵ The role of systemic chemotherapy is currently experimental, with treatment based on regimens for small cell lung carcinoma.²⁶ Following excision, our patient underwent both radiation and chemotherapy for presumed metastatic MCC. Cases of spontaneous tumor regression have been reported,²⁷ and we believe that our patient had a spontaneous regression of the primary lesion prior to diagnosis.

Merkel cell carcinoma has been associated with paraneoplastic syndromes in case reports. It has been found in the anti-Hu antibody syndrome, causing paraneoplastic LE.^{28,29} Merkel cell carcinoma has also been found in cases of Lambert-Eaton myasthenic syndrome, in association with anti-P/Q-type calcium channel antibodies.³⁰ However, our patient was not found to have anti-Hu antibodies or any other antibodies known to be associated with LE.

In our patient, the only antibody detected was anti-N-type calcium channel antibody (at a titer of 0.13 nmol/L). While N-type calcium channel antibodies were found (at a titer of 0.42 nmol/L) in a single case report of a patient with LE,³¹ we do not believe there is evidence that these antibodies had clinical significance in our patient.

We hypothesize that chronic hyponatremia due to ectopic ADH secretion by a neuroendocrine tumor with MCC phenotype was the underlying cause of our patient's cognitive impairment and seizures, resulting in a presentation mimicking LE. Fluid restriction and tumor resection followed by radiotherapy and chemotherapy have resulted in complete remission of her symptoms and malignancy.

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