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Extratemporal FLAIR hyperintensities in anti-Hu paraneoplastic limbic encephalitis A case report and review of the literature

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Abstract

We describe the case of a patient with anti-Hu paraneoplastic limbic encephalitis secondary to small cell lung cancer in whom imaging demonstrated migratory fluid-attenuated inversion recovery (FLAIR) hyperintensities in the frontal, temporal and occipital lobes which resolved with minimal residual gliosis after immunotherapy. Paraneoplastic limbic encephalitis is caused by onconeuronal antibodies to various neuronal antigens, and imaging typically reveals mesial temporal lobe diffusion restriction and FLAIR hyperintensities. Brainstem and cerebellum involvement is often also seen in anti-Hu encephalitis, however, extralimbic cortical involvement is unusual as well as the resolution of such lesions without any residual gliosis. We describe the clinical presentation and neuroimaging and review the literature on paraneoplastic limbic encephalitis.

Keywords

limbic encephalitis; paraneoplastic syndrome; anti-hu antibody; small-cell lung cancer

Abbreviations

FLAIR: Fluid attenuated inversion recovery; EEG: Electroencephalogram; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; CT: Computerized tomography; FDG-PET: Fluorodeoxyglucose positron emission technology; ANNA: Anti-neuronal nuclear antibody; PCR: polymerase chain reaction.

Introduction

Paraneoplastic limbic encephalitis is an autoimmune inflammatory condition characterized by seizures, encephalopathy, memory loss and personality changes. In this condition, tumors express antigens that are shared by native, non-neoplastic neuronal tissues causing antibody formation to these tumor-related antigens and resultant immune-mediated damage [1,2]. As a result, patients present with manifestations of multifocal central and even peripheral nervous system involvement dependent on the type of antibody which is being produced. An enigmatic clinical presentation may precede the diagnosis of the cancer by several months or longer [3]. We present a case of anti-Hu paraneoplastic encephalitis in which the clinical history and neuroimaging was characterized by evanescent non-limbic cortical lesions and an occult primary tumor.

Case Report

A 57 year old woman presented to an outside hospital with episodes of speech arrest followed by left hemifacial numbness. The patient had a longstanding history of tobacco use. EEG showed evidence of seizure and non-contrast brain MRI showed scattered FLAIR-hyperintensities in the bilateral frontal, right parietal and left occipital cortices (Figure 1). CSF analysis showed elevated protein concentration of 61 mg/dL (normal 15-45 mg/dL), normal glucose of 81 mg/dL, 20 white blood cells and 0 red blood cells (0-5) per high-powered field, positive oligoclonal bands with 12 bands in the CSF and 1 band in serum, a CSF IgG level of 7.3 (<8.1) and an elevated IgG index of 1.14 (<0.85). CSF Herpes simplex virus polymerase chain reaction (PCR), CSF Lyme index, and CSF myelin basic protein were negative. Serum Lyme Western blot, HIV antigen/antibody, and rheumatoid factor were also negative. She was started on intravenous methylprednisolone for the working diagnosis of atypical demyelinating disease and discharged. MRI brain performed two weeks later showed an increase in size of cortical lesions and a new lesion in the right frontal lobe (Figure 1). She was started on levetiracetam for episodes of staring and cheek twitching presumed to be seizure.

A few weeks later, she presented again to an outside hospital with convulsive status epilepticus. On arrival, the patient was normotensive with a blood pressure of 129 mmHg systolic and 72 mmHg diastolic. At that time, she had convulsive movements lasting for 35 minutes; she was given lorazepam and phenytoin and required intubation. She was subsequently transferred to our hospital. Multiple anti-epileptic drugs were required to control seizures, and she was also treated with a five-day course of intravenous methyprednisolone 1000 mg followed by an oral steroid taper. She improved and was ex-tubated. Her blood pressures remained normotensive throughout her admission. A repeat lumbar puncture was performed showed 18 nucleated cells in the first tube of CSF and 12 in the last tube, elevated CSF protein concentration of 59 mg/dL, a persistently elevated CSF IgG of 15.7 (0.5-6.1) and greater than 5 oligoclonal bands present in the CSF. Titers for HSV, VZV, Lyme and CMV were negative. Additional serum testing for angiotensin con-verting enzyme, vitamin B12, thyroid stimulating hormone, thyroglobulin antibodies, and anti-thyroid peroxidase antibodies were unremarkable. MR imaging showed regression of FLAIR-hyperintense lesions (Figure 1).

An analysis of paraneoplastic antibodies returned positive for anti-Hu antibodies in the serum which were positive with a titer level of greater than 1:640. Serum antibody testing for anti-Yo, anti-Ri, anti-Ma1 and Ma2, anti-GAD65, anti-LGI1, anti-CASPR, anti-VGCC and anti-VGKC were additionally sent and returned negative. Serum aquaporin-4 antibodies were tested and negative. Chest CT did not demonstrate a lung mass, however 18FDG-PET scan demonstrated 1.8 cm FDG-avid mediastinal lymph node. CT-guided biopsy of that node revealed small cell lung cancer. Platinum-based chemotherapy was begun and both anti-epileptic medications and monthly immunoglobulin therapy were continued, and MRI changes continued to resolve with only a faint amount of residual right frontal gliosis (Figure 1). The patient was discharged to a rehabilitation facility and eventually returned home, but continues to struggle with short-term memory loss and neurocognitive deficits.

Discussion

Irrespective of cause and associated autoantibody, autoimmune encephalitis commonly affects the limbic system. The first diagnostic criteria for paraneoplastic limbic encephalitis was proposed by

Gultekin [4] and includes short-term memory loss, seizures or psychiatric symptoms; four years period between symptom onset and diagnosis of cancer; inflammatory CSF signs, including either T2- or FLAIR-hyperintensity or EEG-abnormality in the temporal lobe and no evidence of other cause for symptoms and signs. MR imaging will often demonstrate hyperintense signal in one or both mesial temporal lobes on FLAIR or T2-weighted sequences, a finding which, while not specific, is considered by many to be an integral part of the criteria supportive of the diagnosis [3]. EEG may show epileptiform discharges in the temporal or extra-temporal regions which may not necessarily correlate to areas of hyperintensity on MRI [5].

Anti-Hu is the most common antibody identified in limbic encephalitis [4]. Also known as anti-neuronal nuclear antibody 1 (ANNA), it is an onconeural antibody directed against RNA-binding proteins in the nuclei and cytoplasm of neuronal cells [1]. Onconeural antibodies form in response to tumors that produce antigenic proteins which are normally only expressed in neural cells. In turn, these antibodies mediate damage to neurons due to their cross-reactivity with normal neuronal Hu proteins [1,2]. While most commonly associated with small-cell lung cancer, anti-Hu has been reported in breast cancer, ovarian dysgerminoma and undifferentiated large-cell carcinoma, among other malignancies [6].

Neurologic symptoms of the paraneoplastic syndrome precede the diagnosis of cancer in 70-80% of patients [7,8]. The initial evaluation for associated neoplasia is negative in 16.5% of patients with anti-Hu antibodies [6], and often tumors which are discovered are small and limited in extent. Dalmau and colleagues reported that 96% of 71 patients with autoantibodies to lung cancer had disease confined to the chest [7]. Cerebrospinal fluid abnormalities are seen in 81% of cases and include pleocytosis and protein elevation; in one case series, cerebrospinal fluid testing for intrathecal IgG synthesis was positive in all 15 patients [4], similar to the persistent IgG synthesis seen in the patient we describe and which is observed in other autoimmune neurologic disorders.

In addition to treatment of an underlying tumor, therapy is directed at suppressing the abnormal immune response and may include a combination of intravenous immunoglobulin or corticosteroids [9]. Additionally, rituximab has been utilized with demonstrated functional improvement [10]; plasma exchange and cyclophosphamide may also be considered [11]. Response to treatment of an underlying neoplasm varies; up to 73% of anti-Hu positive patients improve with treatment of the tumor [4] but many will require assistance with daily activities [12]. The confusional state may be more likely to improve than memory loss or psychiatric manifestations [3].

Imaging findings in Anti-Hu associated encephalitis are limbic-predominant. MRI of the brain often reveals FLAIR hyperintensities in the amygdala and hippocampal formation with extra-limbic involvement being atypical; in one case series of 42 patients with limbic encephalitis, only two cases were not confined to the amygdala and hippocampus [13]. However, extra-limbic involvement such as cerebellar cortical edema and atrophy and brainstem encephalitis are more common in Anti-Hu compared to other autoimmune encephalopathies [2,14], though they can also be seen in Ma-2 associated encephalitis as well as a fulminant form of GABA-receptor encephalitis [15,16].

The striking attribute of this case is the subacute development of extra-limbic, non-enhancing and evanescent cortical and subcortical FLAIR-hyperintensities. The differential diagnosis of these cortical lesions includes subacute infarction from embolism or vasculopathy, posterior reversible

encephalopathy syndrome (PRES), infection, and other systemic autoimmune encephalopathies such as lupus encephalitis or Sjogren's syndrome. Additionally, recent prolonged seizure activity of any etiology has been known to cause transient diffusion-weighted imaging hyperintensities in the thalamus and cerebral cortex [16]. Since the cortically-based lesions did not contrast-enhance, confusion with brain metastases is not likely [17]. Furthermore, unlike metastases, these lesions responded to immunotherapy and treatment of the associated malignancy, leaving behind little or no gliosis [17,18]. The resolution of the lesions would be atypical for ischemic infarction of any etiology. Posterior reversible encephalopathy syndrome is also a consideration with reversible FLAIR hyperintensities, but would typically present in the context of hypertension, which the patient did not have during her hospitalizations; additionally the time course of several months of evolution of symptoms would be atypical for PRES.

Ultimately, despite the unusual extra-limbic distribution of lesions, the patient was diagnosed with paraneoplastic encephalitis on the basis of her antibody testing, subsequent malignancy diagnosis, and symptoms. While extratemporal involvement has been described in the literature in the parietal and frontal cortices [17], to our knowledge our case report is the first to have describe occipital cortical involvement. Furthermore, most cases of extratemporal autoimmune encephalitis are accompanied by limbic involvement on neuroimaging or involve systemic autoimmunity such as Graves' disease[19], unlike the case we present. The absence of limbic, striatal, cerebellar or brainstem lesions, patterns that are often associated with autoimmune encephalopathy [16], adds to the pedagogy of this case.

Figures

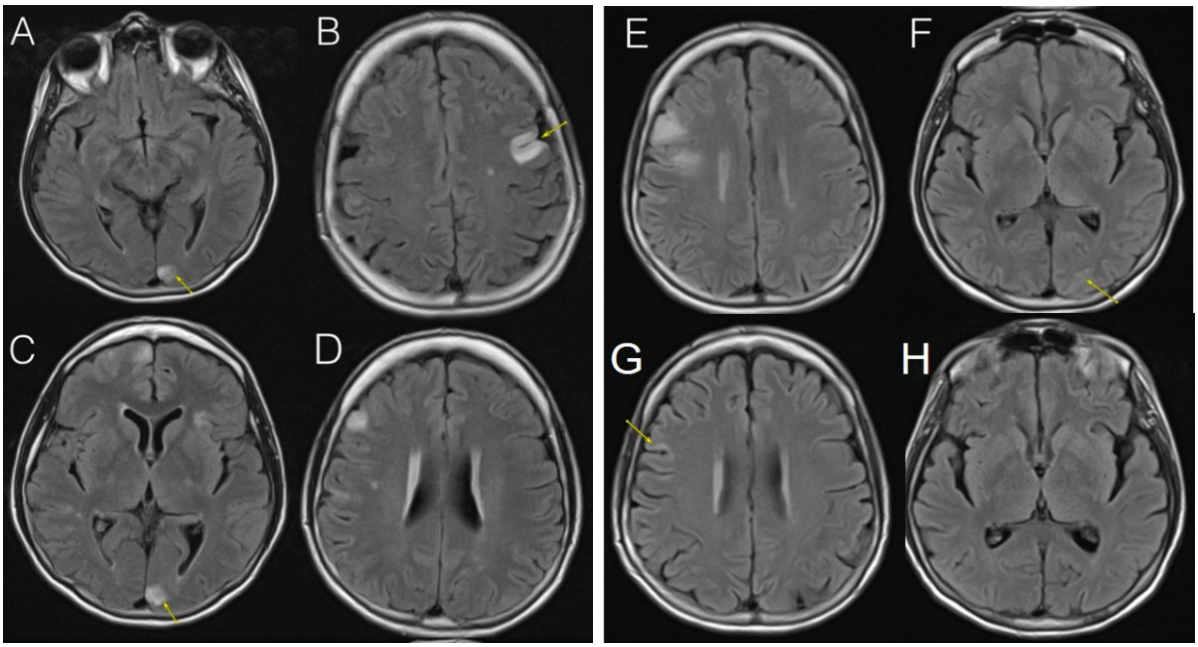

Figure 1: Demonstrates evolution of MRI changes throughout the course of the disease. MRI brain FLAIR sequence on initial presentation with left occipital lesion (A) and left frontal lesion (B); short interval follow-up a few weeks later, after five-day steroid treatment, with persistent occipital lesion (C) and interval development of a new right frontal lesion (D). FLAIR sequence three months after initial presentation, prior to immunotherapy, demonstrating evolution of R frontal lesion (E) and resolution of L occipital lesion (F); FLAIR sequence seven months after initial presentation, after IVIG and chemotherapy administered, with only minimal residual right frontal gliosis (G) and no recurrence of occipital lesion (H).

Conclusion

Limbic encephalitis is an uncommon condition causing seizures, neurobehavioral changes and confusional state; its diagnosis is often elusive given the broad range of clinical presentation. Anti-Hu is the most common cause of paraneoplastic, or malignancy-associated, limbic encephalitis. While typical imaging findings in Hu-associated limbic encephalitis are hyperintensities in the temporal region, extra liimbic involvement can occur in the frontal, parietal, and occipital lobes as well. One unique finding in anti-Hu encephalitis is the complete or near-complete resolution of these T2 and FLAIR hyperintensities after immunotherapy or chemotherapy with no residual gliosis.

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