Reversible Extralimbic Paraneoplastic Encephalopathies With Large Abnormalities on Magnetic Resonance Images

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Objective: To describe reversible extralimbic paraneoplastic encephalopathies with large, lobar lesions on magnetic resonance imaging (MRI).

Design: Case series.

Setting: Autoimmune Neurology Clinic, Mayo Clinic, Rochester, Minnesota.

Results: Three patients had large confluent areas of signal abnormality on T2-weighted MRI, including frontal in 2 and frontal and occipital in 1. Patient 1, a woman aged 63 years, experienced hemiparesis with hemianopia 3 years after a diagnosis of adenocarcinoma of the breast. Nine years later, rapidly progressive dementia developed. Patient 2, a woman aged 79 years, presented with monoparesis and epilepsia partialis continua, 1 year after a diagnosis of adenocarcinoma of the breast. Patient 3, a man aged 65 years, had paraneoplastic sensory neuropathy, limbic encephalitis, antineuronal nuclear autoantibody type 1 (ANNA-1), and squamous cell carcinoma of the lung. He was stable for 3 years after treatment. Subacute onset of aphasia, delirium, worsening seizures, and rising ANNA-1 titers led to a diagnosis of recurrent limited carcinoma. Brain MRI abnormalities in all patients improved dramatically after immunotherapy. Two patients had sustained clinical remission.

Conclusion: Recognition of paraneoplastic extralimbic lobar encephalopathies is important because these disorders and their underlying cancers are treatable.

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Several focal paraneoplastic disorders of the central nervous system are readily recognized, including limbic encephalitis,1 cerebellar degeneration,2 and brainstem encephalitis.3 Among larger numbers of patients with more classic presentations, some case series of paraneoplastic neurological disorders have tabulated a few patients whose focal or multifocal encephalopathies involved the cerebral hemispheres beyond the limbic system. Examples include supratentorial and extratemporal encephalopathic manifestations in patients with antineuronal antibodies and thymoma,4 N-methyl-D-aspartate receptor antibodies and teratoma,5 antineuronal nuclear autoantibody type 1 (ANNA-1, also known as anti-Hu antibody) and small cell carcinoma,6 ANNA-2 (anti-Ri antibody) and small cell or breast carcinoma,7 and less well-characterized autoantibodies.8 Lobar extralimbic paraneoplastic encephalopathies have received less attention than more classic presentations.

Herein we describe in detail 3 patients who had lobar, extralimbic, paraneoplastic encephalopathies; large T2-weighted signal abnormalities on magnetic resonance imaging (MRI); limited cancer; and favorable responses to immunotherapy.

REPORT OF CASES

Details of serological, cerebrospinal fluid, and electrophysiological tests and duration of follow-up are reported in the Table.

PATIENT 1

A 63-year-old woman presented with balance and visual difficulties 3 years after treatment for locally invasive adenocarcinoma of the breast. Results of an examination revealed a mild left-sided hemiparesis and left-sided homonymous hemianopia. Findings on MRI (Figure 1A) were remarkable for a large, confluent, nonenhancing, right-sided parietal and occipital T2-weighted abnormality. Examination of a biopsy specimen showed nonspecific abnormalities only (microglial reaction and scant perivascular lymphocytes). After a short course of oral dexamethasone, complete clinical and near-complete radiological resolution occurred (Figure 1B). After 9 years of complete remission from her neurological symptoms, the patient presented...
with a rapidly progressive dementia (Kokmen Short Test of Mental Status score, 13 of 38) characterized by declining attention, memory, and executive function associated with left-sided frontal and occipital nonenhancing T2-weighted white matter abnormalities (Figure 1C). Results of an extensive systemic search for cancer were negative. A diagnosis of a relapsing autoimmune, paraneoplastic encephalopathy was made. The patient declined a further brain biopsy and was treated with 1000 mg of intravenous methylprednisolone for 5 days, followed by 1000 mg every 2 weeks for 6 weeks. A dramatic improvement in the Kokmen score (to 36 of 38) and resolution of the radiological abnormalities occurred within 6 weeks of commencing treatment (Figure 1D). Remission was maintained 6 months after completing treatment.

PATIENT 2

A 79-year-old woman presented with subacute onset of weakness and twitching of the right limbs 1 year after completing treatment for locally invasive breast adenocarcinoma. Results of the neurological examination showed prominent myoclonus and ideomotor apraxia of the right upper extremity and mild right-sided hemiparesis. A neurodegenerative cause (corticobasal degeneration) was considered in the early evaluation, but MRI revealed a confluent area of abnormality of the white matter of the left superior-posterior frontal lobe with mild gyral swelling and subtle gyral enhancement (Figure 2A-C). Evaluations for potential causes, including focal infection, were negative. A focal, paraneoplastic encephalopathy with epilepsy partialis continua was diagnosed. The patient received a 5-day course of intravenous methylprednisolone followed by 6 treatments of monthly intravenous cyclophosphamide. Clinical stabilization was still evident 6 months after completing cyclophosphamide treatment.

Table. Oncological, Serological, CSF, and EEG Findings and Duration of Follow-up for the 3 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cancer Type, Site</th>
<th>Paraneoplastic Serological Findings and Titers</th>
<th>CSF Abnormalities</th>
<th>EEG Findings</th>
<th>Duration of Follow-up From First Evaluation, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma of the breast</td>
<td>None</td>
<td>Protein level, 49 mg/dL (first presentation), 47 mg/dL (second presentation); 2 nucleated cells/µL; no CSF oligoclonal bands</td>
<td>Right posterior epileptiform discharges (first presentation)</td>
<td>Mild right-sided posterior focal slowing (first presentation)</td>
</tr>
<tr>
<td>2</td>
<td>Adenocarcinoma of the breast</td>
<td>None</td>
<td>Protein level, 62 mg/dL; 1 nucleated cell/µL; 5 CSF oligoclonal bands</td>
<td>Left-sided central perirolandic epilepsy partialis continua</td>
<td>Mild, nonspecific left-sided central slowing; 2 self-limited focal motor seizures recorded</td>
</tr>
<tr>
<td>3</td>
<td>Squamous cell carcinoma of the lung</td>
<td>CSF: ANNA-1, 1:128 (first remission); 1:1024 (second attack); serum: ANNA-1, 1:15360 (first attack); 1:960 (first remission); 1:3840 (second attack)</td>
<td>2 Nucleated cells/µL; protein level, 77 mg/dL; 2 CSF oligoclonal bands</td>
<td>Multifocal spikes, sharp waves and intermittent PLEDs over the left-sided frontal, temporal, and midline frontal regions</td>
<td>Focal slowing, spikes, and sporadic sharp waves over the left-sided temporal region only</td>
</tr>
</tbody>
</table>

Abbreviations: ANNA-1, antineuronal nuclear autoantibody type 1 (anti Hu); CSF, cerebrospinal fluid; EEG, electroencephalography; PLED, periodic lateralizing epileptiform discharge.

- Reference range, 14 to 45 mg/dL.
- Reference limit, less than 6.
- Reference limit, less than 4.
- Reference limit, less than 1:2.
- Reference limit, less than 1:120.
however, frequent right-sided focal motor seizures were apparent despite antiepileptic medication therapy. At that time, MRI demonstrated near-complete resolution of the frontal white matter abnormality (Figure 2D).

PATIENT 3

A 65-year-old man presented initially with immunotherapy-responsive sensory and autonomic neuropathy and limbic encephalitis in the setting of ANNA-1 seropositivity. Three years after onset of the neurological symptoms, continued cancer surveillance revealed squamous cell carcinoma of the lung. After lobectomy and radiotherapy, the patient achieved neurological and oncological remission, but MRI abnormalities of the left side of the hippocampus and amygdala persisted. Three years later, acute word-finding difficulties heralded a generalized tonic-clonic seizure, despite adherence to an antiepileptic medication regimen (phenytoin sodium, 300 mg/d, and levetiracetam, 3000 mg/d). Complex partial seizures were frequent and characterized by loss of awareness, staring, and occasional right-sided limb jerking. Examination results showed mild delirium and loss of verbal fluency. Magnetic resonance imaging demonstrated new, extensive cortical T2-weighted signal abnormality of the left frontal and right parietal regions with patchy gyriform enhancement (Figure 3A–C). Relapsing paraneoplastic encephalopathy, predominantly affecting the left frontal lobe, was diagnosed. After plasma exchange, he received oral cyclophosphamide for 1 year and continued his previous medication regimen. Complete resolution of neuro-

logical abnormalities (clinical and radiological) was noted (Figure 3D–F). Recurrent squamous cell carcinoma (a right-sided hilar mass) was found at completion of immunotherapy and treated with chemotherapy and radiation. In 2 subsequent years of follow-up, the cancer, seizures, and encephalopathy remained in remission, but orthostatic hypotension persisted.

The 3 patients described herein represent cases of reversible autoimmune, paraneoplastic encephalopathies with extralimbic lobar MRI abnormalities. The focal and unilateral MRI appearance may be mistaken for a neoplastic or infectious process and prompted initial brain biopsy in patient 1. Clues to an autoimmune process included: (1) a history of cancer (all patients); (2) relapsing course (2 patients); (3) oligoclonal bands in the cerebrospinal fluid (1 patient; no patient had cerebrospinal fluid pleocytosis); (4) detection of a paraneoplastic autoantibody (1 patient); and (5) remarkable clinical or radiological response to immunotherapies (all patients).

Focal extralimbic paraneoplastic encephalopathy has been described previously in individual case reports or as rare occurrences among larger series of limbic encephalitis cases. Porta-Etessam et al described a patient with focal motor facial seizures, cognitive impairment with frontal features, and noneenhancing right-sided frontal T2-weighted MRI abnormalities. Small cell carcinoma of the lung (and ANNA-1 antibodies) was found in that patient. The patient died 3 months later, after treatment with antiepileptic medication only. Vernino and Lennon described 12 patients who developed encephalitis in the context of thymoma: 9 had typical limbic encephalitis and 3 presented with multifocal clinical and radiological involvement of the cerebral cortex. Neuronal autoantibodies (ganglionic acetylcholine receptor, voltage-gated potassium channel, glutamic acid decarboxylase 65, collapsin response-mediator protein 5–IgG, or ANNA-1 antibodies) were detected in 11 of those patients. Among the 20 patients with ANNA-1 antibodies and cortical encephalitis described by Graus et al, all but 3 had limbic encephalitis. Clinical and radiological frontal lobar involvement was noted in 3 of 12 women with N-methyl-D-aspartate receptor antibodies and resolved in 2 after teratoma removal or immunotherapy. Considerable improvements in facial twitching and laryngospasm were noted in a woman with breast cancer, ANNA-2 antibodies, and a nonehancing right-sided insular cortex lesion after combined oncologic treatment and immunotherapy.

Clinical seizures were evident in 2 patients in our series, and all patients had epileptiform abnormalities on electroencephalography that improved in each case after treatment. Although antiepileptic medications were used in 2 patients, clinical improvement correlated best with initiation of immunotherapies. Although the history of cancer predated the onset of neurological symptoms in all patients, the onset of a predominantly left-sided frontal lobe encephalopathy heralded recurrence of cancer in patient 3. The presence of ANNA-1 autoantibodies and cancer history successfully
directed the cancer search in this patient, exemplifying the predictive oncological value of paraneoplastic serological findings, irrespective of neurological presentation. An interval increase in the serum or the cerebrospinal fluid titer of a preexisting neural autoantibody (ANNA-1 in this instance) sometimes has positive predictive value for relapse of the neurological disease or cancer.

In summary, paraneoplastic lobar encephalopathies may be extratemporal in location and may initially suggest an infectious or invasive neoplastic process. Accurate diagnosis is important to optimize the chance for clinical stabilization or improvement with timely immunotherapy.

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Author Contributions: Study concept and design: McKeon and Pittock. Acquisition of data: McKeon and Ahlskog. Analysis and interpretation of data: McKeon, Britton, Lennon, and Pittock. Drafting of the manuscript: McKeon. Critical revision of the manuscript for important intellectual content: Ahlskog, Britton, Lennon, and Pittock. Administrative, technical, and material support: Lennon. Study supervision: Pittock.

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