Neoplastic Meningitis and Paraneoplastic Syndromes

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KEYWORDS

• Neoplastic meningitis • Paraneoplastic syndromes • Leptomeningeal metastasis
• Limbic encephalitis • Anti-NMDAR encephalitis

KEY POINTS

- Neoplastic meningitis (NM) is an uncommon metastatic manifestation of cancer, characterized by multifocal neurologic signs and symptoms.
- In a suspected case of NM, work-up includes detailed clinical examination, MR imaging of the brain and entire spine with and without contrast, cerebrospinal fluid analysis and pressure measurement, and systemic imaging, staging, and restaging of the primary tumor with PET–computed tomography or MR imaging.
- Paraneoplastic syndromes (PNSs) are a group of disorders present in patients with cancer, which may involve any part of the nervous system (central and peripheral nervous disorders) and simultaneously may affect multiple areas.
- PNSs encompass a variety of symptoms or syndromes, including limbic encephalitis, cerebellar degeneration, brainstem encephalitis, striatal encephalitis, and opsoclonus-myoclonus syndrome.

INTRODUCTION

Neoplastic meningitis (NM) is an uncommon metastatic manifestation of cancer, characterized by multifocal neurologic signs and symptoms and usually occurring late in the course of the disease. Diagnosis is challenging but essential to prevent progressive neurologic injury that substantially impairs cancer patients' quality of life. Clinical examination has a minimal role in the diagnosis of NM. The most common tests employed are the brain and spinal axis MR imaging and cerebrospinal fluid (CSF) cytology.

The incidence of NM varies, depending on the primary site of the tumor. NM is diagnosed in 4% to 15% of patients with solid tumors (carcinomatous meningitis), 5% to 15% of patients with hematological malignancies (leukemic or lymphomatous meningitis), and 1% to 2% of patients with primary brain tumors.[1–4] NM is associated with significant morbidity and short survival rates, ranging from several weeks to 8 months. Adenocarcinoma is the most frequent histology, whereas among the solid tumors, breast, lung, and skin are the most common primary sites of leptomeningeal metastasis. Although small cell lung carcinoma (SCLC) and melanoma have the highest rates of spread to the leptomeninges, with 11% and 20%, respectively, breast cancer, because of its higher incidence, accounts for most disorder cases despite a 5% metastatic rate.[5–7] Lymphomatous meningitis is reported most commonly with diffuse high-grade non-Hodgkin lymphoma. Prophylactic treatment commonly is considered in patients with aggressive non-Hodgkin lymphoma, such as Burkitt lymphoma and lymphoblastic lymphoma, because these diseases have a greater than 25% risk of meningeal relapse without central nervous system (CNS)-directed therapy. NM is the initial manifestation of systemic cancer in only 5% to 10% of patients.[2] Synchronous

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intraparenchymal brain metastases are evident in 11% to 31% of patients with NM.[8]

PATHOPHYSIOLOGY

For NM to occur, tumor cells must reach the meninges and CSF. The invasion of the meninges occurs through different pathways, depending on the histology of the primary tumor. These include hematogenous (venous or arterial) spread, neural spread (endoneuronal and perineural), perivascular lymphatic spread, and iatrogenic spread.[9,10] In addition, spread may occur directly from brain parenchyma or bony tumor lesions in the skull, spine, or choroid plexus or from de novo tumors. All routes give tumor cells access to the subarachnoid space of the CNS. With regard to hematogenous spread, tumor cells in the bloodstream become lodged in small-caliber CNS vessels, resulting in ischemia distal to the affected vessel. This disrupts vessel endothelium and surrounding basement membranes, allowing tumor cells to access the CSF around the damaged vessel (the Virchow-Robin space) and the subarachnoid space.[9,10] Tumor cells can gain access to the ventricular system by invading the subependymal lining of the ventricular wall.

The threshold number of tumor cells necessary to reach the CSF and result in clinical NM is unknown. The location of the tumor, however, plays a vital role in the spread. The closer proximity of the tumor to the meninges leads to a higher incidence of NM. Medulloblastomas (tumors located in or near the fourth ventricle) and pineoblastoma (near the pineal gland) are notable examples of this principle.[11] Astrocytomas are not a significant cause of NM. Postoperative NM, presumably caused by intraoperative tumor cell seeding of the CSF, has been reported in 5% to 40% of patients after craniotomy. The risk of NM is higher in patients undergoing craniotomy for posterior fossa metastases than supratentorial metastases.[12]

CLINICAL FEATURES

Clinical diagnosis of NM is challenging, and sufficient suspicion is required to warrant diagnostic testing. A majority of patients present with multifocal neurologic symptoms that vary according to anatomic areas of the CNS: cerebrum (15% of patients), cranial nerve/brainstem (35%), and spinal cord (60%)[13,14] (**Table 1**). Cerebral symptoms include headache, dizziness/vertigo, confusion, fatigue, gait instability, aphasia, altered mental status, seizure, hemiparesis, and numbness. The most common of these manifestations are headache and mental status changes.[1,2,13–15] When the posterior fossa is the primary site of the NM, most clinical symptoms are due to cerebellar dysfunction; these include unsteady gait, diplopia, ataxia, and falls. Cranial nerve lesions are reported in approximately 40% of patients.[1,2,13–15] The most common dysfunctions are of the oculomotor, facial, cochlear, and optic nerves. Cranial nerve and brainstem symptoms include loss of visual acuity, diplopia, facial muscle weakness, hearing loss, dysphagia and dysarthria, hoarseness, decreased hearing, and facial pain or numbness. Diplopia is the most common symptom of cranial nerve dysfunction, with cranial nerve VI the most frequently affected, followed by cranial nerves III and IV.[1,2,13–16] Symptoms involving the spinal cord may include lumbar pain, limb paresis or paralysis, bowel and bladder dysfunction, and loss of reflexes leading to cauda equine or cauda medullaris syndrome.

One of the most common complications of NM is communicating hydrocephalus due to blockage of the basal cisterns and obstruction to CSF absorption at the arachnoid granulation level.[9,17] Less common complications are basal ganglia or internal capsule infarctions due to vascular compression and development of vasculitis, with vasospasm and thrombosis from exudate surrounding small perforating vessels. These are seen more commonly in pediatric patients.

DIAGNOSIS

NM is diagnosed using the National Comprehensive Cancer Network guidelines.[18] Diagnosis is established on positive CSF cytology for malignant cells, and/or leptomeningeal and nodular enhancement on computed tomography (CT) or MR imaging in a patient with known malignancy. There are ongoing efforts by Response Assessment in Neuro-Oncology (the Leptomeningeal Assessment in Neuro-Oncology scorecard) and the European Association of Neuro-Oncology–European Society of Medical Oncology to standardize the diagnostic work-up and interpretation of NM.[19,20] These groups use clinical symptoms, imaging, and CSF analysis for diagnosis and assessment of treatment. Unfortunately, neither of the 2 systems has been validated.

In a suspected case of NM, work-up includes detailed clinical examination, MR imaging of the brain and entire spine with and without contrast, CSF analysis and pressure measurement, and systemic imaging, staging, and restaging of the primary tumor with PET-CT or MR imaging. Although positive CSF cytology provides the highest degree of certainty in an NM diagnosis, it is not

Table 1
Major neurologic symptoms of neoplastic meningitis

Cerebral symptoms	Headache Mental changes Nausea Vertigo Vomiting Seizures Communicating hydrocephalus Gait alterations Coordination disorders
Cranial nerve dysfunction	Diplopia Vision loss Hearing loss Facial paresis Hoarseness Hypoacusia Ocular motility deficits Dysphagia
Spinal symptoms	Bilateral/unilateral pain Loss of reflexes Paresthesia Motor deficits Weakness in extremities

essential for initiating treatment if the remainder of the evaluation is supportive of NM.

Diagnosis of NM largely depends on documenting circulating tumor cells in the CSF.[21] The site of the CSF tap and yield depend on the symptoms and type of the primary malignancy. Cytology of CSF obtained by lumbar puncture is more likely to be positive than CSF obtained from ventricles if spinal cord–related symptoms are present and vice versa if cranial-related symptoms are present.

CSF abnormalities include increased opening pressure (>200 mm of H_2O), increased leukocytes (>4/mm^3), elevated protein (>50 mg/dL), and decreased glucose (<60 mg/dL). These findings may be suggestive of NM but do not confirm a diagnosis.[14,19] CSF cytology may be positive in only 45% of the cases on the first lumbar puncture, with an increase in yield up to 80% with a second CSF examination. Each subsequent lumbar puncture has a poor yield of only 2%.[14,19]

Imaging plays a vital role and is the initial investigation of choice in a suspected case of NM. Contrast-enhanced (CE) MR imaging of brain (**Fig. 1**) and axial skeleton remains the most sensitive imaging modality for diagnosis, with sensitivity of 76% and specificity of 77% in patients with supportive clinical findings.[19,22] Bacterial, fungal, or viral meningeal inflammation, neurosarcoidosis, chronic meningitis, and Guillain-Barré syndrome may mimic NM; therefore, it is important to correlate the imaging findings with the appropriate clinical setting.

On MR imaging, noncontrast fluid-attenuated inversion recovery (FLAIR) images show hyperintensity within the sulci and cisterns due to increased CSF proteinaceous content (**Fig. 2**A). Contrast-enhanced T1-weighted imaging (T1WI) or magnetization-prepared rapid acquisition of gradient echo (MPRAGE) demonstrates subarachnoid, ventricular, or parenchymal enhancing nodules; focal or diffuse pial enhancement; and ependymal, sulcal, folial, or cranial nerve enhancement (**Fig. 2**B).[19,22,23] Postcontrast 3-dimensional T2-FLAIR images provide higher sensitivity in detecting leptomeningeal abnormalities than conventional postcontrast T1 images or postcontrast MPRAGE.[24] The most frequent brain MR imaging findings are subarachnoid nodules and pial enhancement. Due to dependency, enhancement commonly is appreciated around the basal cisterns and over the surface of the midbrain, pons, and over the cerebellar folia. Enlargement and enhancement of the cranial nerves are seen, most commonly within the oculomotor, facial, cochlear (**Fig. 3**), and optic nerves (**Fig. 4**). Most typically, enhancement is seen along the cisternal segments of the cranial nerves. Enhancement and dysfunction of cranial nerves III, IV, and VI are common causes of diplopia in patients with NM (**Fig. 5**).

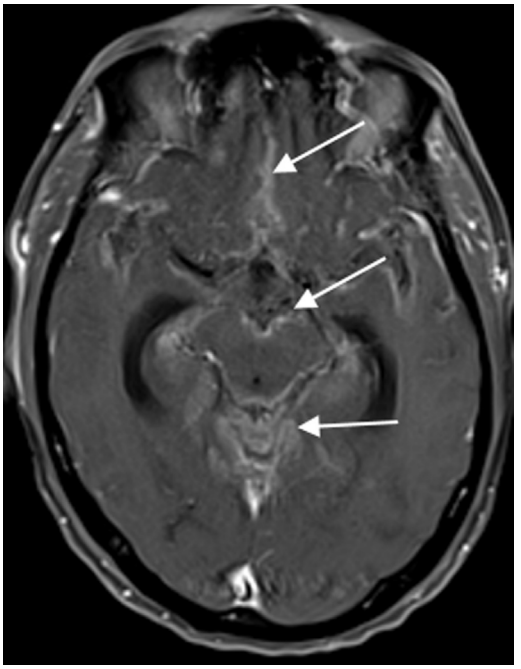

Fig. 1. Contrast-enhanced T1WI shows diffuse leptomeningeal enhancement (*arrows*) over the cerebral cortex, along the basal cisterns and cerebellar folia in a patient with breast cancer.

MR imaging also is sensitive for detecting metastatic deposits along the neuraxis. CE MR imaging of the spine shows smooth leptomeningeal enhancement or intradural extramedullary enhancing nodules, especially in the lumbar spine and over the cauda equine (**Fig. 6**).[25] Lumbosacral nerve root thickening and enhancement commonly is observed on CE MR imaging of the lumbar spine. Studies have suggested that MR imaging–proved leptomeningeal seeding is an indicator of poor prognosis and could be used to identify responses to intrathecal chemotherapy. Microscopic metastases, however, are below the resolution of MR imaging; therefore, cytology has a higher rate of specificity but a lower rate of sensitivity.

In highly suspected cases of neoplastic meningitis with negative CSF and imaging examination, other tests, such as CSF immunohistochemical examinations, polymerase chain reactions, fluorescence in situ hybridization, and cytogenetic analysis, can improve the detection rate.[26,27] Tumor-specific markers—such as carcinoembryonic antigen for adenocarcinomas, α-fetoprotein, and β-human chorionic gonadotropin for germ cell tumors; 5-hydroxyindoleacetic acid for carcinoid tumors; and immunoglobulins for multiple myeloma—are employed very rarely for the NM diagnosis.[19,28] Nonspecific tumor markers, such as vascular endothelial growth factor, creatine kinase–BB isoenzyme, tissue polypeptide antigen, and lactate dehydrogenase isoenzyme-5, can be strong indirect indicators of NM. None is sensitive enough, however, to improve on the cytologic diagnosis. In certain malignancies like leukemia or lymphoma, the sensitivity of flow cytometry is several degrees higher than that of cytology for detecting CSF leukemia or lymphoma.

Hydrocephalus remains one of the most common complications of the NM due to blockage of the basal cisterns and obstruction to CSF absorption at the arachnoid granulation level (**Fig. 7**).[10,29] Placement of a ventriculoperitoneal shunt is an effective palliative approach in patients with symptomatic hydrocephalus. An Ommaya reservoir or similar devices, useful in administering intraventricular chemotherapy and CSF sampling, are employed routinely in NM patients. These devices are safer and more comfortable for the patient than

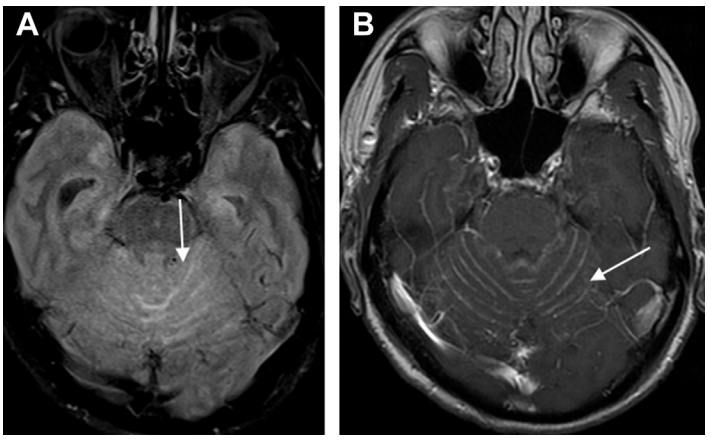

Fig. 2. Breast cancer with NM. Axial FLAIR image (*A*) shows hyperintensity within the cerebellar folia (*arrow*) due to increased CSF proteinaceous content. Axial postcontrast T1WI (*B*) shows leptomeningeal enhancement along the folia (*arrow*).

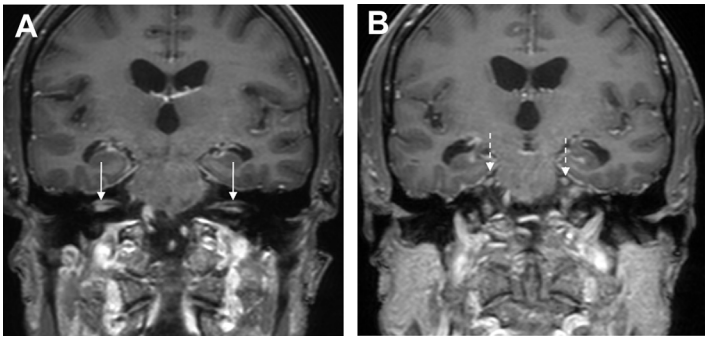

Fig. 3. Lung cancer patient presented with bilateral sensory-neural hearing loss. Contrast-enhanced coronal T1WIs show bilateral enhancement of the VII-VIII nerve complex (*arrows* [*A*]) and enhancement of the bilateral trigeminal nerves (*dotted arrows* [*B*]).

repeated lumbar punctures and help in the uniform distribution of the drug in the CSF.[10,29,30] It is crucial to ensure that the catheter's tip and side perforations are inserted entirely into the ventricle to avoid drug instillation into the brain parenchyma. This placement needs to be confirmed with a CT scan to avoid chemotherapy related leukoencephalopathy. Other complications include reservoir malfunction and infection. Underdiagnosis and assessing response to treatment remain significant problems in NM patients when the CSF and imaging tests are negative.

Early diagnosis and treatment of NM are vital because most untreated patients die within 1 week to 9 weeks (median 3 weeks) due to neurologic disease and tumor progression. The main aim of treatment is to extend survival and stabilize or improve neurologic symptoms. To date, brain and neuraxis imaging and CSF analysis remain the backbone of investigations in a suspected case of NM.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes (PNSs) are a group of disorders that present in patients with cancer. PNSs may involve any part of the nervous system (central and peripheral nervous disorders) and may affect multiple areas simultaneously. PNS is a rare neurologic disorder seen approximately in 0.01% of cancer patients.[31] PNS incidence largely depends on the tumor cell type. Approximately 30% of patients with thymoma have some form of neurologic autoimmunity, mostly myasthenia gravis, compared with pulmonary small cell carcinoma, which is associated with 1 or more PNSs in 3% of cases.[32,33] Other malignancies associated with PNSs include gynecologic malignancies arising from the breast, ovary, fallopian tube, and peritoneum; Hodgkin lymphoma and non-Hodgkin lymphoma; testicular cancer; and neuroblastoma. PNSs occur at a much lower rate in patients with larger cell lung, renal, uterine, and melanotic skin cancers.

PNSs encompass a variety of symptoms or syndromes, including limbic encephalitis, cerebellar degeneration, brainstem encephalitis, striatal encephalitis, and opsoclonus-myoclonus syndrome (**Box 1**).[31,34,35] Myelitis, motor neuron disease, stiff person syndrome, Lambert-Eaton myasthenic syndrome (LEMS), neuromyotonia, and Guillain-Barré syndrome also are included. Manifestations precede the diagnosis of cancer in many cases.

Paraneoplastic encephalopathy is an autoimmune-mediated disorder associated with various specific antibodies. Tumor-targeted immune responses are initiated by onconeuronal

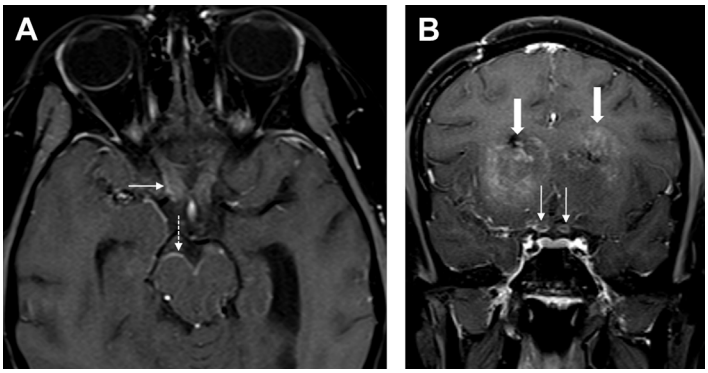

Fig. 4. Bilateral vision loss in a patient with CNS lymphoma. Axial (*A*) and coronal (*B*) postcontrast fat-saturated T1WIs show circumferential enhancement of the bilateral optic nerves (*arrows*) due to leptomeningeal metastasis (*thin dash arrow*). Note bilateral frontal lobe lymphoma across the corpus callosum (*fat arrows* [*B*]).

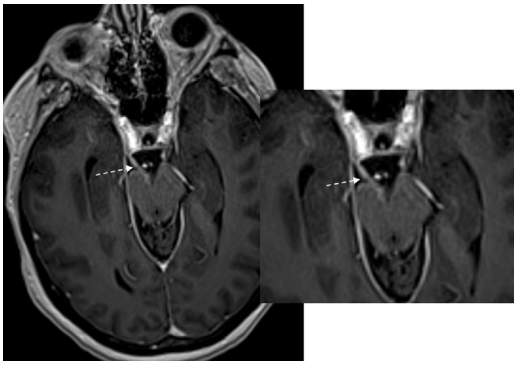

Fig. 5. A 21-year-old male patient with leukemia presented with a history of diplopia. Axial contrast-enhanced T1WI (*A*) and magnified view at the level of midbrain (*B*) show enhancement over the midbrain's surface and along the right third cranial nerve (*arrow*).

proteins expressed within the neoplasm (neoplastic cells) at the plasma membrane, nucleus, cytoplasm, or nucleolus. These antigens also are expressed in neurons or glia (coincidental targets). This leads to paraneoplastic neurologic syndrome by means of immune cross-reaction.

There are 2 main type antibodies: antibodies to intracellular antigens and antibodies to cell-surface antigens (**Table 2**).[34–38] The former includes Hu (antineuronal nuclear antibody type 1 [ANNA-1]), Ri (antineuronal nuclear antibody type 2 [ANNA-2]), antineuronal nuclear antibody type 3, anti-antiglial/neuronal nuclear antibody, Yo (Purkinje cell cytoplasmic antigen type 1 [PCA-1]), Purkinje cell cytoplasmic antigen type 2 (PCA-2), Ma1, Ma2, CV2/collapsing response mediator protein type 5 [CRMP-5], zinc finger transcription factor (Zic4), Tr, amphiphysin, and glutamic acid decarboxylase (GAD). The latter includes *N*-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel (VGKC), leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid receptor (AMPAR), P/Q-types and N-type calcium channel, neuromyelitis optica, glycine receptor, acetylcholine (Ach) receptor, γ-aminobutyric acid B1 receptor ($GABA_BR$), and metabotropic glutamate receptor-5. Antibodies targeting intracellular antigens are targeted by cytotoxic T cells; histopathology is characterized by CD4 and CD8 lymphocyte T-cell infiltration. Histopathology of antibodies to the cell surface or synaptic antigens is characterized by B-lymphocyte and plasma cell infiltration, leading to antibody and complement deposition.

Clinical presentation of the PNSs largely depends on the primary target in the nervous system. Because some symptoms may precede the cancer diagnosis, imaging, especially when positive, plays an important role in PNS diagnosis. MR imaging brain remains the primary imaging of choice in a suspected case of PNS. In many suspected cases, the MR imaging can be normal, but image findings and clinical presentations help narrow the range of antibody tests to be ordered. Imaging appearance depends on the primary targets in the brain parenchyma. A typical pattern seen on MR imaging findings includes limbic encephalitis, cerebellar degeneration, brainstem encephalitis, striatal encephalitis, and myelitis/myelopathy.[35–38] Other commonly performed investigations are electroencephalogram (EEG) and CSF examination. EEG can show diffuse slowing of electrical activity with or without spikes indicative of heightened cortical irritability.[39] CSF examinations serve 2 primary purposes: to rule out infection, neoplasm, and other primary pathologies and to document the antibody.

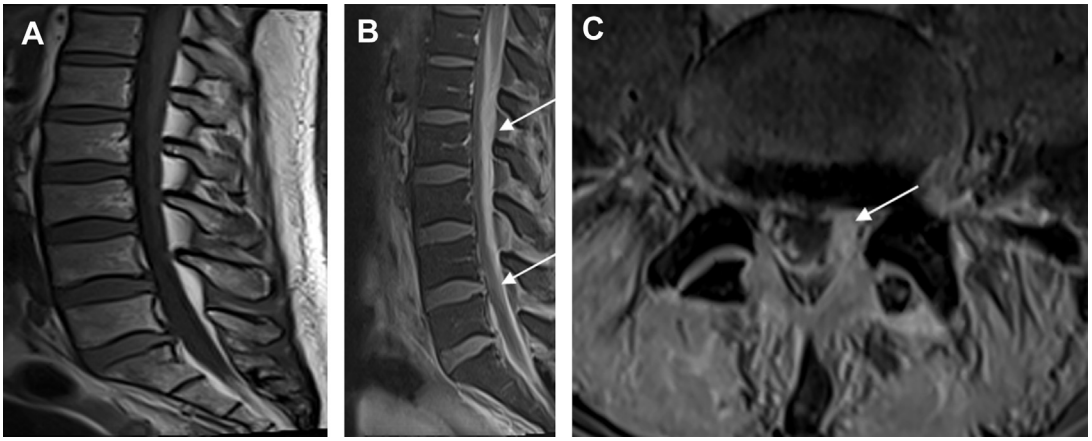

Fig. 6. Leptomeningeal enhancement along the cauda equine and filum terminale in a patient with breast cancer. Precontrast sagittal T1 (*A*), postcontrast sagittal T1 (*B*), and axial T1 (*C*) show diffuse enhancement along the filum terminale (*arrows* in *B*) and intraspinal nerve roots (*arrow* in *C*).

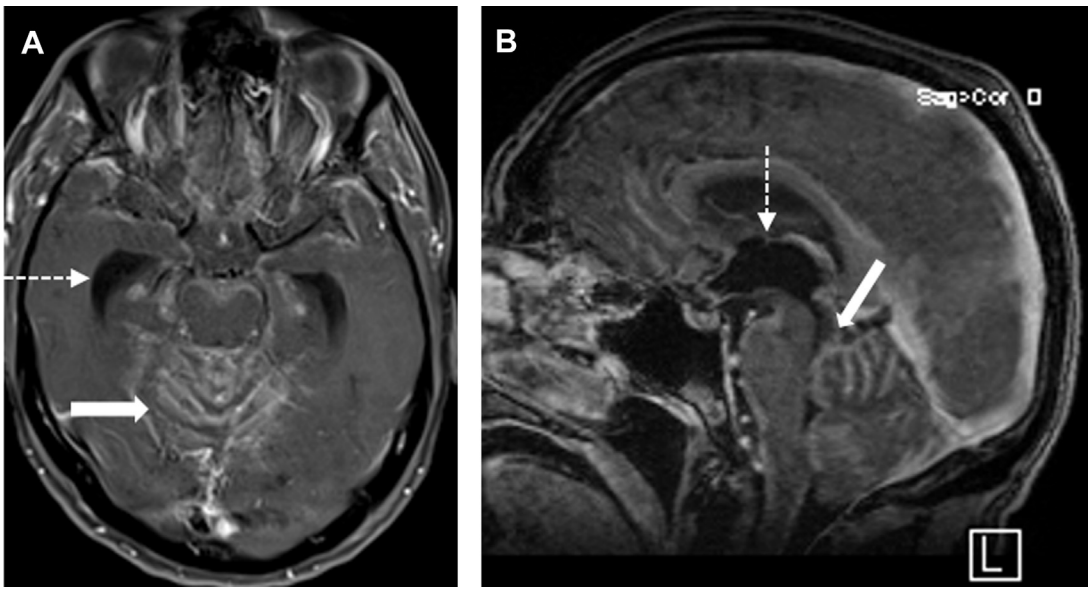

Fig. 7. Obstructive hydrocephalus due to NM in a patient with breast cancer. Postcontrast axial (*A*) and sagittal T1WIs (*B*) show diffuse, a thick enhancement (*thick arrow*) over the cerebellar folia, basal cisterns, and aqueduct, leading to dilatation of the temporal horns and third ventricle (*dash arrow*).

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is a common PNS resulting from tumor induced autoimmunity against cerebellar antigens. There are more than 30 different antibodies associated with this condition with anti-Yo (PCA-1) antibody the most common.[40,41] In men, many reported tumors are adenocarcinomas of the gastrointestinal system and prostate. PNS has been seen with a variety of other antibodies, including Hu, Ri, Tr, Zic4, mGluR1, and voltage-gated calcium channels (VGCCs).[40,41] Patients present with nonspecific gait unsteadiness, which progresses to severe cerebellar ataxia over a few weeks or months. Other symptoms include cognitive and psychiatric morbidity, notably memory loss and emotional lability.

MR imaging of the brain often is normal in the early stages, but global volume loss in both the vermis and cerebellar hemispheres with relative sparing of the brainstem is seen in later stages (**Fig. 8**). A superior cerebellar hyperintense sign on FLAIR image also has been reported.[42] The underlying mechanism for this atrophy is believed to be an immunologic reaction to cerebellar degeneration-related protein 2, a protein found in the cerebellum that is produced ectopically by tumor cells.[40,41]

Autoimmune limbic encephalitis (ALE) is an inflammatory disease involving the limbic system, predominately in the medial temporal lobes. It commonly is associated with SCLC, breast cancer, and ovarian tumors, including teratoma, testicular tumor, and thymic tumor.[31,34,38] It also may be seen with colon cancer, pancreatic cancer, renal cell cancer, esophageal cancer, bladder cancer, prostate cancer, neuroblastoma, melanoma, and Hodgkin lymphoma and non-Hodgkin lymphoma. ALE involves intracellular antigen antibodies (anti-Ma2, Hu, and CV2/CRMP-5, GAD) and neuronal surface antibodies (NMDAR, VGKC, AMPAR, and $GABA_BR$) with or without tumor association.[31,34,38,39,43,44] The clinical picture of limbic encephalitis is characterized by rapid development of confusion, working memory deficit, mood changes, anxiety, depression, psychosis, and seizures. The subacute development of short-term memory loss is considered the hallmark of the disorder but is often overlooked because of other symptoms.

MR imaging remains the imaging modality of choice for ALE. It often shows increased signal on T2-weighted FLAIR imaging in the medial aspect of the temporal lobes (**Fig. 9**).[45,46] This abnormality more often is bilaterally asymmetric than unilateral. Involvement of the basal ganglia usually is noted whereas involvement of the lateral temporal lobe and insula is less common. In addition, there is lack of restricted diffusion and hemorrhages in ALE. Various other pathologies, such as herpes encephalitis, postictal edema, hypoglycemia, stroke, and tumors, may involve the medial temporal lobes. Early diagnosis and differentiation from viral encephalitis are vital for treatment. In herpes encephalitis, T2 hypersensitivity on MR imaging is seen involving the cortical and the

Box 1
Paraneoplastic disorders

- Brain
  - Paraneoplastic encephalomyelitis
  - Limbic encephalitis
  - Brainstem encephalitis
  - Opsoclonus-myoclonus
  - PCD
  - Chorea
- Eye
  - Paraneoplastic optic neuritis
  - Paraneoplastic retinal degeneration
- Spinal cord
  - Myelopathy
  - Myelitis with rigidity and spasms
  - Motor neuronopathy
  - Acute necrotizing myelopathy
- Nerves
  - Sensory neuronopathy
  - Sensorimotor peripheral neuropathy
  - Autonomic neuropathy, gastrointestinal dysmotility
  - Motor neuronopathy
- Neuromuscular junction/muscle
  - LEMS
  - Myasthenia gravis
  - Dermatomyositis
  - Neuromyotonia
- Muscle
  - Polymyositis/dermatomyositis
  - Acute necrotizing myopathy
- Multifocal disorders
  - Encephalomyeloneuropathies

subcortical regions of the bilateral temporal lobes, frontal lobes, and insula.[45,46] Restricted diffusion, gyral swelling, loss of gray-white matter interface, and mild or no enhancement also are associated. Petechial hemorrhages, when present, strongly favor herpes encephalitis over limbic encephalitis. Involvement of extratemporal regions, such as the cingulate gyrus and frontal lobes, are not uncommon. Postictal edema also can cause temporal lobe T2 hyperintensities and swelling. The lack of prodromal neuropsychiatric symptoms and the resolution of temporal lobe changes after cessation of seizure activity are supportive of seizure-related MR imaging changes rather than ALE. Ischemic stroke involving the medial temporal lobe usually presents acutely but sometimes causes only mild neurocognitive deficits.

CSF examination mainly is helpful to exclude mimics of ALE, in particular herpes encephalitis. Polymerase chain reaction testing for the herpes simplex virus in the CSF has high diagnostic sensitivity and specificity, but clinicians should be wary that it may be negative early in the disease course. The clinical presentation of acute herpes encephalitis is very different from that of ALE.

Brainstem Encephalitis

Paraneoplastic brainstem encephalitis can occur in association with limbic encephalitis, in isolation, or as the predominant clinical manifestation of paraneoplastic neuronal disorder (PND). This clinical syndrome is characterized by multiple cranial nerve palsies, long tract signs, and cerebellar ataxia. Less common features include movement disorders, such as parkinsonism, chorea, jaw opening dystonia, and myoclonus. Brainstem encephalitis commonly is seen in young men with testicular cancer (anti-Ma2).[31,47] Anti-Ri, anti-Hu, anti-Tr, and anti-NMDAR are less common causes of paraneoplastic brainstem encephalitis.[34–36,38,47] MR imaging shows patchy hyperintensity in the brainstem and/or basal ganglia on T2 or FLAIR images but rarely shows enhancing nodules on postcontrast scans (**Fig. 10**). Differential diagnoses include infectious brainstem encephalitis, tumor infiltration, vasculitis, and demyelinating disease.

Striatal Encephalitis/Paraneoplastic Chorea

Striatal encephalitis is a rare paraneoplastic encephalopathy. It is seen in anti-CV2/CRMP5 encephalitis cases associated with SCLC and thymoma.[48,49] The pattern can be seen in other paraneoplastic encephalopathies, including anti-VGKC, anti-NMDAR, and anti-Hu antibodies.[48,49] As the name suggests, MR imaging abnormality of the T2 hyperintensity is seen in the bilateral caudate nuclei and putamina; it also may be associated with limbic encephalitis and cerebellar degeneration. Differential diagnoses include infectious encephalitis, toxic and metabolic diseases, Sydenham chorea, Huntington disease, Wilson disease, and Creutzfeldt-Jakob disease.

OTHER PARANEOPLASTIC DISORDERS

Although some PND has unique features, others may be indistinguishable from common neurologic

Table 2
Neuronal paraneoplastic autoantibodies associated paraneoplastic neuronal disorders and tumors

Group I antibodies: autoimmune encephalitis with intracellular antigens		
Anti-Hu (ANNA1) anti-Hu	LE, sensory neuronopathy, autonomic and sensorimotor neuropathies	SCLC (may be seen with thymoma, or neuroblastoma)
Anti-Ma2	LE, BSE	Testicular seminoma (young patients) SCLC or breast cancer (older patients)
Anti-Ma1	BSE, PCD	Lung cancer
Anti-CV2/CRMP-5	Movement disorder (chorea) and ocular syndromes (uveitis, optic neuritis)	SCLC and thymoma
Anti-Ri antibody (ANNA-2)	Opsoclonus-myoclonus syndrome, BSE, PCD	Breast cancer, SCLC, and gynecologic malignancies
Anti-PCA 2	Encephalomyelitis, PCD,	SCLC
Anti-Yo antibody	PCD	Ovarian or breast malignancy
Anti-Tr	PCD	Hodgkin disease
Anti-amphiphysin	Stiff person syndrome,	SCLC
GAD	LE	Thymoma, SCLC
Group II antibodies: autoimmune encephalitis with cell-surface antigens or antibodies against synaptic receptors		
Anti-NMDAR	LE, hyperactivity, seizures, and memory change, psychiatric symptoms	Ovarian teratoma
Anti-VGKC	limbic encephalitis, neuromyotonia	SCLC, thymoma, prostatic cancer
Anti-VGCC	LEMS, PCD	SCLC
Anti-AMPAR	LE	Thymoma, SCLC
Anti- $GABA_BR$	LE	SCLC
Anti-mGluR1	PCD	Hodgkin lymphoma
LGI1	LE	Thymoma
Anti-ACh receptor	MG	Thymoma

Abbreviations: BSE, brainstem encephalitis; LE, limbic encephalitis; MG, myasthenia gravis.

disorders. Description of symptoms of PND depends on the site involved in the nervous system, commonly depending on multiple organelles. Neurologic presentations are classified depending on the anatomic site in.

Spinal cord presentations include myelopathy, myelitis with rigidity and spasms (stiff person syndrome), paraneoplastic sensory neuronopathy, and motor neuronopathy.[38,50] Spinal cord–related symptoms typically are in combination with other PND, such as limbic or brainstem encephalitis. Symptoms depend on the anatomic cells or area involved within the spinal cord. As the name suggests, stiff person syndrome is characterized by axial and proximal lower limb stiffness and spasms and is associated with anti-GAD antibodies or anti-amphiphysin antibodies in breast cancer.[38,50,51] Rapidly progressive motor neuron disease is associated with anti-Hu antibodies whereas primary lateral sclerosis is seen in breast cancer patients.

The peripheral nervous system is involved far more commonly than the CNS and presents with neuropathies. Sensory neuronopathies are more common than motor neuropathies in PND. Malignancies may present either isolated or combined with other neuropathies. Hodgkin disease patients can present with acute inflammatory demyelinating polyradiculoneuropathy whereas non-Hodgkin lymphoma cases present with a subacute lower motor neuronopathy as a slowly progressive lower motor neuron syndrome affects the lower limbs. Neuromyotonia is an unusual manifestation of cancer characterized by muscle cramps, stiffness, twitching, sweating, and abnormal

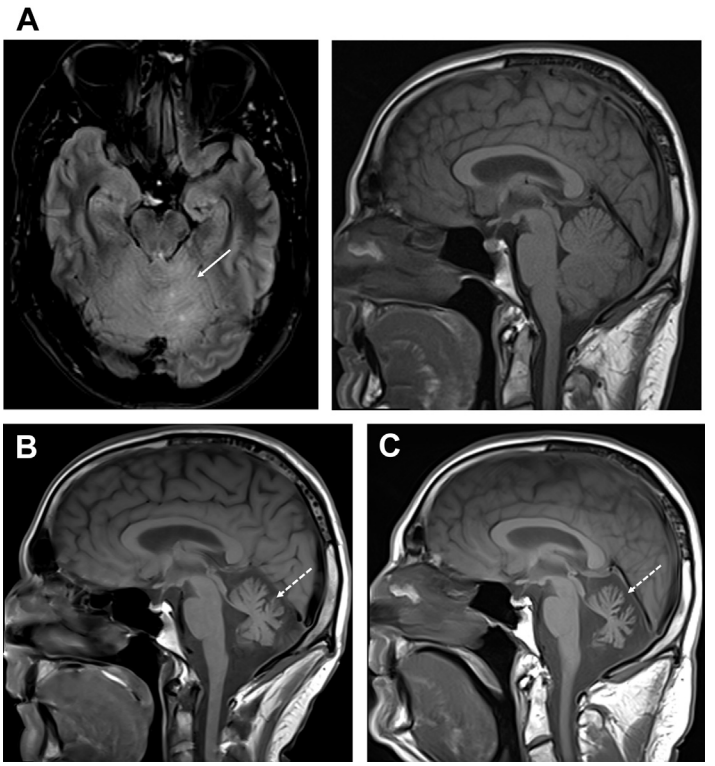

Fig. 8. PCD in a 56-year-old patient with adenocarcinomas of colon. Axial FLAIR and sagittal T1WIs (2014 [*A*]) show subtle superior cerebellar hyperintensity on FLAIR image (*arrow*) with normal volume. Sagittal T1WIs (MRI in 2017 [*B*] and MRI in 2019 [*C*]) show progressive global volume loss in both the vermis and cerebellar hemispheres (*arrows* in Band C).

relaxation after voluntary contraction. It is associated with thymomas and SCLC and involves antibodies against VGKCs.

LEMS is a paraneoplastic or primary autoimmune neuromuscular junction disorder characterized by proximal weakness and autonomic dysfunction.[52] It is caused by the presence of antibodies generated against the P/Q-type VGCCs on presynaptic nerve terminals that decrease the release of Ach.[52–54] A majority of LEMS cases are associated with SCLC, which expresses functional VGCCs. LEMS may be seen in other

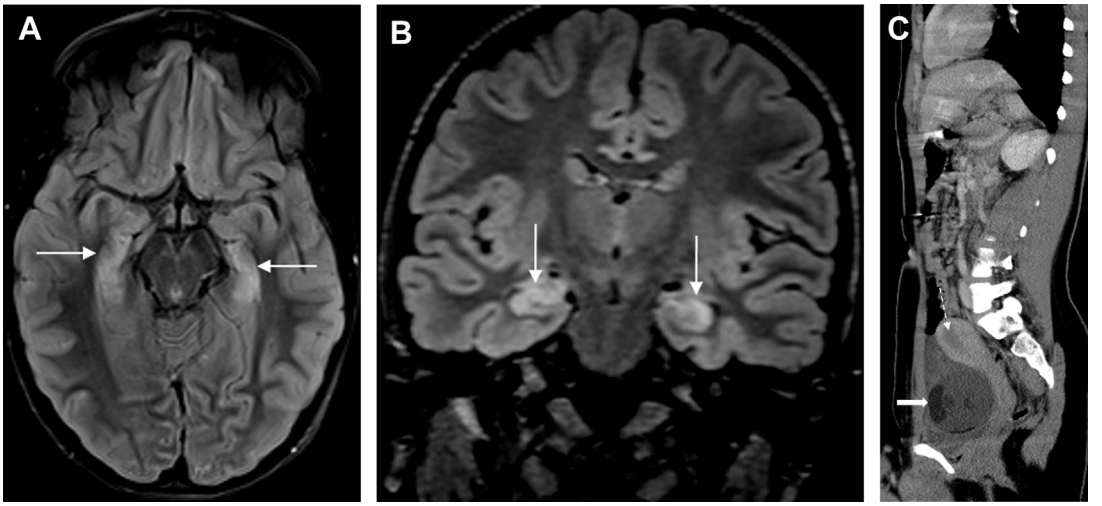

Fig. 9. Limbic encephalitis in a 28-year-old woman with ovarian teratoma. Axial (*A*) and coronal (*B*) FLAIR images show bilateral hyperintensity and mild enlargement of the hippocampus proper (*arrows*). Sagittal reconstructed image through the pelvis shows an ovarian mass with a fat signal (*arrow*). Note normal stretched uterus (*dash arrow*) due to mass effect.

malignancies, such as non–small cell and mixed lung carcinomas, prostate carcinoma, thymoma, and lymphoproliferative disorders.

Clinically, patients present with proximal muscle weakness, predominantly affecting lower limbs; areflexia; and autonomic disturbances, such as impotence, constipation, and dry mouth. Clinical presentation of LEMS may precede cancer diagnosis by months. The LEMS diagnosis is based on clinical features in patient with lung malignancies. The confirmation of a diagnosis is based on the detection of specific VGCC antibodies. P/Q VGCC antibodies are present in 80% to 90% of patients with LEMS.[55]

EVALUATION OF THE PARANEOPLASTIC NEURONAL DISORDER

PND diagnosis requires a multidimensional approach, high clinical suspicion, CSF and serum examination for routine and specific autoantibodies, and imaging.[34,36,38] Neuroimaging is an integral part in the evaluation of PND in the CNS but generally does not contribute to the diagnosis of PND in the peripheral nervous system. Besides MR imaging of brain and spinal cord, CT or MR imaging of the chest, abdomen, and pelvis are mandatory in suspected cases to determine the presence and location of underlying malignancies.[44] When the primary malignancy is unknown, the search initially may be focused on tumor types commonly associated with the patient's syndrome or type of antineuronal antibody. If the tumor found does not histologically match the syndrome or antibody, a search for a second neoplasm should be undertaken. Because PNS onset often precedes the cancer diagnosis or occurs when the tumor is small and difficult to detect, a multidisciplinary approach to a cancer diagnosis is warranted. In such cases, PET scans can be useful to locate the primary tumor. Mammograms, transvaginal ultrasounds, and, in rare instances, exploratory laparotomies may be performed in selected cases. In cases of an initial tumor screen that is negative, patients should be followed at regular intervals with scans (eg, every 6 months for the next 4 years). If there is a strong clinical suspicion of PNS, but imaging tests are negative, cancer screenings should be repeated periodically depending on the type of disorder. A patient with a confirmed diagnosis of LEMS with no malignancy documented on CT, MR imaging, or PET screening should continue to be screened every 3 months to 6 months for at least 2 years.[52,53] For classical PNSs with anti-Hu antibodies related to SCLC should be screened for every 6 months. For disorders with anti-NMDAR encephalitis, less frequent and shorter durations are reasonable (eg, evaluation for ovarian teratoma yearly for 2 years). In more than 90% of patients with solid tumors and PNS, the tumor is found within 1 year of PNS presentation.

ANTIBODY TESTING

The detection of specific autoantibodies remains crucial in establishing a diagnosis of autoimmune encephalitis. Documentation of these autoantibodies under the appropriate clinical findings helps to make the diagnosis of the immunologic subtypes of encephalitis. Onconeuronal and GAD antibodies are present in the serum and CSF; they are detectable with many techniques, including ELISA, immunoblotting, and immunohistochemistry.[34–36,38,44] It is advisable to include both CSF and serum for neuronal antibody testing in patients with suspected autoimmune encephalitis. Between the 2 tests, CSF examinations remain paramount because relevant antibodies may be found only in the CSF (anti-NMDAR encephalitis);

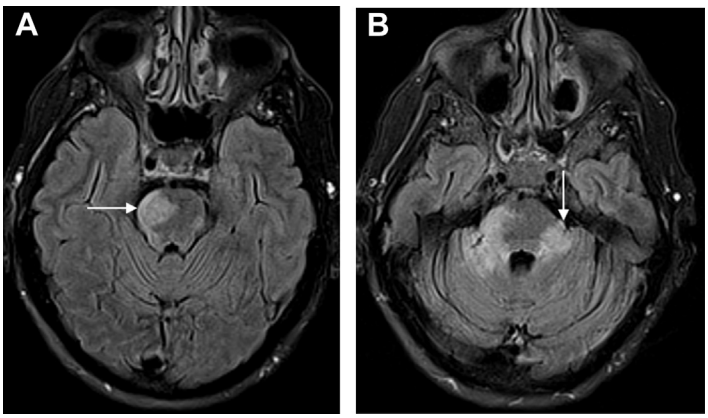

Fig. 10. Paraneoplastic brainstem encephalitis due to SCLC. Axial flair images (*A, B*) show patchy hyperintensity in the pons (*arrow* in *A*) and partly involving the middle cerebellar peduncles (*arrow* in *B*).

the antibody concentration in the CSF correlates better with the clinical course than antibody concentrations in the serum; the repertoire of antibodies in the CSF and serum can be different in the same patient (eg, NMDAR in CSF and serum and γ-aminobutyric acid type A ($GABA_A$) receptor only in serum); the types of antibodies in the CSF usually determine the clinical picture, and false-positive and false-negative results are less common with CSF analysis.

SPECIAL ANTIBODIES AND PARANEOPLASTIC ENCEPHALITIS

Group I Antibodies: Autoimmune Encephalitis with Intracellular Antigens

Group I antibodies that target intracellular neuronal antigens are associated closely with underlying malignancies. These antibodies employ the same mechanisms used by cytotoxic T cells to target intracellular neuronal antigens and onconeuronal antigens in the immune response to cancer. Group I antibodies have a decreased response to immunomodulatory therapy and an increased prevalence of irreversible neuronal damage, which leads to poor clinical outcomes. The most clinically relevant group I antibodies include anti-Hu, anti-Ma (Ta), anti-CV2/CRMP-5, anti-Ri, and anti-Yo.[34–36,38,44]

Anti-Hu antibody, also known as ANNA-1, is the most common paraneoplastic form of autoimmune encephalitis.[35–37] It is seen most commonly with SCLC and clinically presents with sensory neuropathy. Anti-Hu antibodies can be seen in patients with extrapulmonary small cell carcinoma, thymoma, or neuroblastoma.[56,57] A subset of patients with anti-Hu encephalitis can present with epilepsia partialis continua, motor seizures involving the face and distal extremities. MR imaging shows T2-FLAIR hyperintense lesions in the medial temporal lobes (**Fig. 11**) and variable involvement of the cerebellum and brainstem.

Anti-Ma (Ta) encephalitis is strongly associated with testicular tumors in young men and SCLC or breast cancer in older patients.[31,46] Neurologic symptoms are due to the involvement of the limbic, diencephalic, or brainstem dysfunction, which presents with limbic encephalitis and brainstem-related ophthalmoplegia (**Fig. 12**).

Anti-CV2/CRMP-5 is associated with SCLC and thymoma. Movement disorder (chorea) and ocular syndromes (uveitis and optic neuritis) are distinctive features.[44] On MR imaging T2-FLAIR, hyperintensity is seen in the striatum without restricted diffusion on diffusion-weighted imaging–apparent diffusion coefficient, differentiating it from Creutzfeldt-Jakob disease, which shows restricted diffusion.

The anti-Ri antibody is associated with breast cancer, SCLC, and gynecologic malignancies. Opsoclonus-myoclonus syndrome, brainstem encephalitis, and PCD have been described with this antibody.[44]

The anti-Yo antibody is the primary cause of PCD. It targets intracellular antigens in the Purkinje cells of the cerebellar cortex, leading to cerebellar degeneration.[44] It commonly is seen in women, associated with ovarian or breast malignancy, and clinically presents with subacute onset ataxia, nystagmus, and dysarthria. MR imaging shows diffuse cerebellar atrophy without brainstem atrophy.

Group II Antibodies: Autoimmune Encephalitis with Cell-surface Antigens

Group II antibodies target cell-surface neuronal antigens and are less likely to be associated with an underlying malignancy. Antibodies often target synaptic proteins and can result in the downregulation of receptors leading to altered synaptic transmission associated with epileptiform activity.

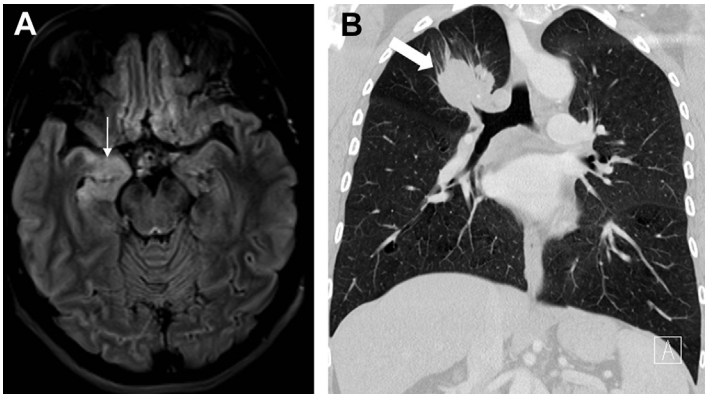

Fig. 11. Anti-Hu antibody limbic encephalitis due to SCLC. Axial FLAIR image (*A*) shows hyperintensity in the right medial temporal lobe (*arrow*). The coronal reconstructed image of the chest (*B*) shows a mass lesion (*arrow*) in the right upper lobe, biopsy-proved SCLC.

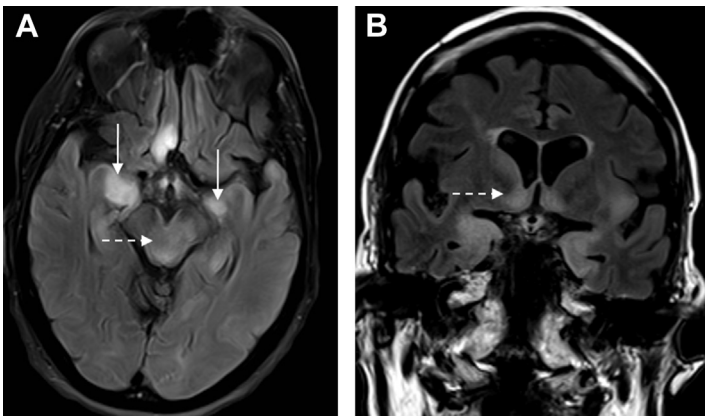

Fig. 12. Anti-Ma encephalitis from testicular tumors in a 29-year-old man. Axial (*A*) and coronal (*B*) FLAIR images show asymmetric hyperintensity in the medial temporal lobes (*arrows*), midbrain (*dash arrow* in *A*), nucleus accumbens (*dash arrow* in *B*), and paraterminal gyrus.

Anti-NMDAR encephalitis

NMDAR encephalitis is a common autoimmune encephalitis classically seen in young women and children with autoimmunity not associated with cancer.[44,58] A minority of NMDAR encephalitis cases, such as ovarian teratoma, can be associated with an underlying malignancy. This highlights the need to screen all patients with autoimmune encephalitis for an underlying malignancy regardless of the antibody profile. This form of the disease is associated with CSF IgG antibodies against the GluN1 subunit of the NMDAR.[44,58] Children usually present with irritability, hyperactivity, seizures, and memory change whereas the adults present with prodromal headache, psychiatric symptoms, fever, and gastrointestinal or upper respiratory symptoms. Motor or complex seizures develop at early stages, but their frequency decreases with disease evolution.

Diagnosis is obtained mostly through documentation of IgG antibodies against the GluN1 subunit of the NMDAR. The other commonly employed test is EEG, which shows a characteristic pattern, the extreme delta brush.[44,58,59] Even though a suspected patient routinely is neuroimaged, MR imaging brain remains normal in 80% to 90% of cases. When MR imaging is positive, a wide variation in the distribution and degree of T2-FLAIR hyperintense signal changes throughout the brain can be seen. Hyperintensities may involve the temporal lobe, insular cortex, and cingulate gyrus.[60,61] The classic patterns of limbic encephalitis, cerebellitis, brainstem encephalitis, and striatal encephalitis are rare.

VGKC encephalitis is another group II subtypes of autoimmune encephalitis and presents with classic features of limbic encephalitis and the development of medically intractable epilepsy.[34,36,37] These clinical features are explained by the high concentration of potassium channels in the limbic structures. Imaging features include T2-FLAIR hyperintensities in the medial temporal lobes, unilaterally or bilaterally, in the acute stages, with a propensity to develop chronic findings of mesial temporal sclerosis on follow-up imaging. Extralimbic involvement in VGKC encephalitis is rare. Although considered a nonparaneoplastic, 5% to 30% of cases have associated tumors (SCLC, thymoma, or prostatic cancer).[34,37,62,63]

Other antibodies associated with paraneoplastic disorders include anti-AMPAR (Glu R1 and GluR2) in patients with limbic encephalitis.[34,36,37] They are seen predominately in patients with lung, breast, or thymus tumors. Anti-$GABA_BR$ encephalitis is seen with SCLC and usually exhibits the limbic encephalitis pattern.[34,36,37] Like other cell-surface antigen-mediated syndromes, such as anti-AMPAR and anti-$GABA_BR$ encephalitis, respond to immunotherapy. The anti-Tr antibody is associated with Hodgkin lymphoma and may show features of limbic encephalopathy and cerebellar or brainstem syndrome.

DISCLOSURE

None.

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