

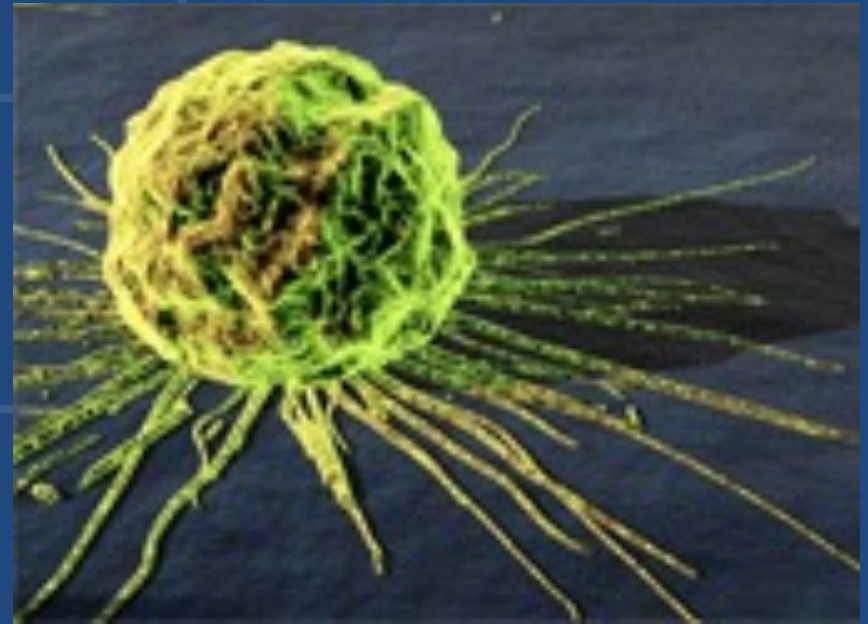


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PARANEOPLASTIC NEUROLOGIC SYNDROMES

PARANEOPLASTIC NEUROLOGIC SYNDROMES

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system.



PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

SYNDROMES OF THE BRAIN, BRAINSTEM, AND CEREBELLUM

Focal encephalitis

Cortical encephalitis

Limbic encephalitis

Brainstem encephalitis

Cerebellar dysfunction

Autonomic dysfunction

Paraneoplastic cerebellar degeneration

Opsoclonus-myoclonus

SYNDROMES OF THE SPINAL CORD

Subacute necrotizing myelopathy

Motor neuron dysfunction

Myelitis

Stiff-person syndrome

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

SYNDROMES OF DORSAL ROOT GANGLIA

Sensory neuronopathy

MULTIPLE LEVELS OF INVOLVEMENT

Encephalomyelitis^a, sensory neuronopathy, autonomic dysfunction

SYNDROMES OF PERIPHERAL NERVE

Chronic and subacute sensorimotor peripheral neuropathy

Vasculitis of nerve and muscle

Neuropathy associated with malignant monoclonal gammopathies

Peripheral nerve hyperexcitability

Autonomic neuropathy

^aIncludes cortical, limbic, or brainstem encephalitis, cerebellar dysfunction, myelitis

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

SYNDROMES OF THE NEUROMUSCULAR JUNCTION

Lambert-Eaton myasthenic syndrome

Myasthenia gravis

SYNDROMES OF THE MUSCLE

Polymyositis/dermatomyositis

Acute necrotizing myopathy

SYNDROMES AFFECTING THE VISUAL SYSTEM

Cancer-associated retinopathy (CAR)

Melanoma-associated retinopathy (MAR)

Uveitis (usually in association with encephalomyelitis)

PARANEOPLASTIC NEUROLOGIC SYNDROMES

They are remote effects of cancer, caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

In 60% of patients the neurologic symptoms precede the cancer diagnosis.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

PATHOGENESIS

Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeurological antigens) expressed by tumors.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

The neurologic manifestations may signal the presence of a tumor long before it would otherwise be detected, permitting early removal.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

PATHOGENESIS

In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified.

PARANEOPLASTIC ANTINEURONAL ANTIBODIES, ASSOCIATED SYNDROMES AND CANCERS

ANTIBODY	SYNDROME	ASSOCIATED CANCERS
Anti-Hu (ANNA-1)	PEM (including cortical, limbic, brainstem encephalitis, cerebellar dysfunction, myelitis), PSN, autonomic dysfunction	SCLC, other neuroendocrine tumors
Anti-Yo (PCA-1)	PCD	Ovary and other gynecologic cancers, breast
Anti-Ri (ANNA-2)	PCD, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecological, SCLC
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-Zic	PCD, encephalomyelitis	SCLC and other neuroendocrine tumors
Anti-CV ₂ /CRMP5	PEM, PCD, chorea, peripheral neuropathy, uveitis	SCLC, thymoma, other

Note: PEM: paraneoplastic encephalomyelitis; PCD, paraneoplastic cerebellar degeneration; PSN, paraneoplastic sensory neuronopathy; SCLC, small-cell lung cancer.

PARANEOPLASTIC ANTINEURONAL ANTIBODIES, ASSOCIATED SYNDROMES AND CANCERS

ANTIBODY	SYNDROME	ASSOCIATED CANCERS
Anti-Ma proteins ^a	Limbic, hypothalamic, brainstem encephalitis (infrequently PCD)	Germ-cell tumors of testis, lung cancer, other solid tumors
Anti-NR1/NR2 subunits of NMDA receptor	Encephalitis with prominent psychiatric symptoms, seizures, hypoventilation	Ovarian teratoma
Anti-amphiphysin	Stiff-person syndrome, PEM	Breast, SCLC
Anti-VGCC ^b	LEMS, PCD	SCLC, lymphoma
Anti-AChR ^b	MG	Thymoma

^a*Patients* with antibodies to Ma2 are usually men with testicular cancer. Patients with additional antibodies to other Ma proteins are men or women with a variety of solid tumors.

^b*These* antibodies can occur with or without a cancer association.

Note: PEM: paraneoplastic encephalomyelitis; PCD, paraneoplastic cerebellar degeneration; PSN, paraneoplastic sensory neuronopathy; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; VGCC, voltage-gated calcium channel; AchR, acetylcholine receptor; SCLC, small-cell lung cancer; NMDA, N-methyl-D-aspartate.

PARANEOPLASTIC ANTINEURONAL ANTIBODIES, ASSOCIATED SYNDROMES AND CANCERS

ANTIBODY	SYNDROME	ASSOCIATED CANCERS
Anti-VGKC ^b	Peripheral nerve hyperexcitability (neuromyotonia), limbic encephalitis	Thymoma, SCLC, others
Anti-recoverin	Cancer-associated retinopathy (CAR)	SCLC and other
Anti-bipolar cells of the retina	Melanoma-associated retinopathy (MAR)	Melanoma

^bThese antibodies can occur with or without a cancer association.

Note: VGKC, voltage-gated potassium channel; SCLC, small-cell lung cancer.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

PATHOGENESIS

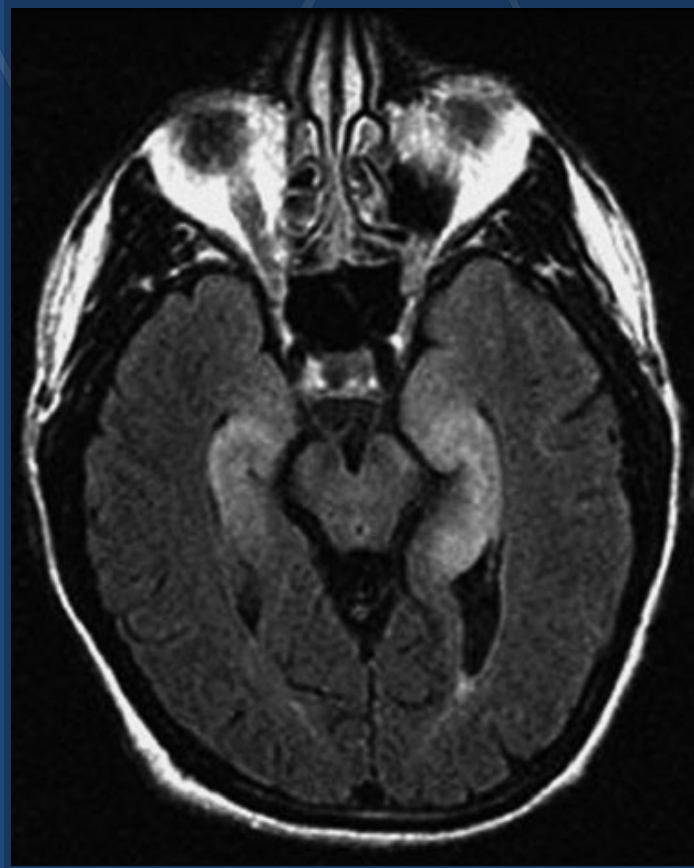
These antibodies usually react with the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) strongly predicts the presence of cancer.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

PATHOGENESIS

Plasma exchange or immunomodulation with intravenous immunoglobulin (IVIg) usually produces neurologic improvement.

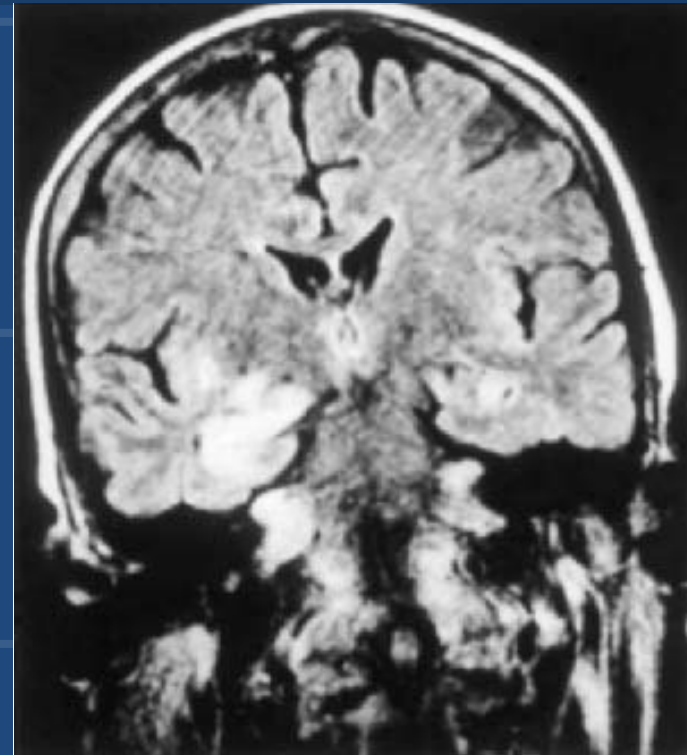
Fluid-attenuated inversion recovery sequence MRI of a patient with limbic encephalitis and voltage-gated potassium channel antibodies



Abnormal hyperintensity involving the medial aspect of the temporal lobes.

PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS

The affected patients are young women who develop combinations of psychiatric symptoms, seizures, dyskinesias, stupor and hypoventilation.

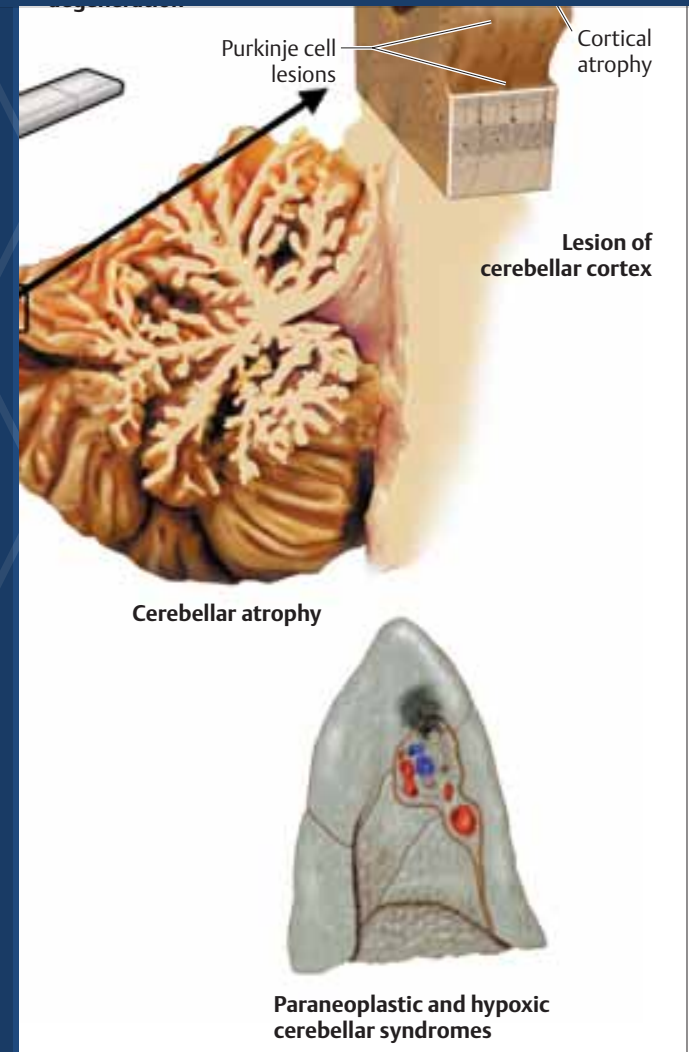


Coronal FLAIR MRI from a woman with paraneoplastic “limbic encephalitis” associated with lung cancer and a mild pleocytosis but no detectable autoantibodies. The hippocampi and adjacent regions are involved. Pathologically there proved to be gliosis and a minimal inflammatory infiltrate in these regions.

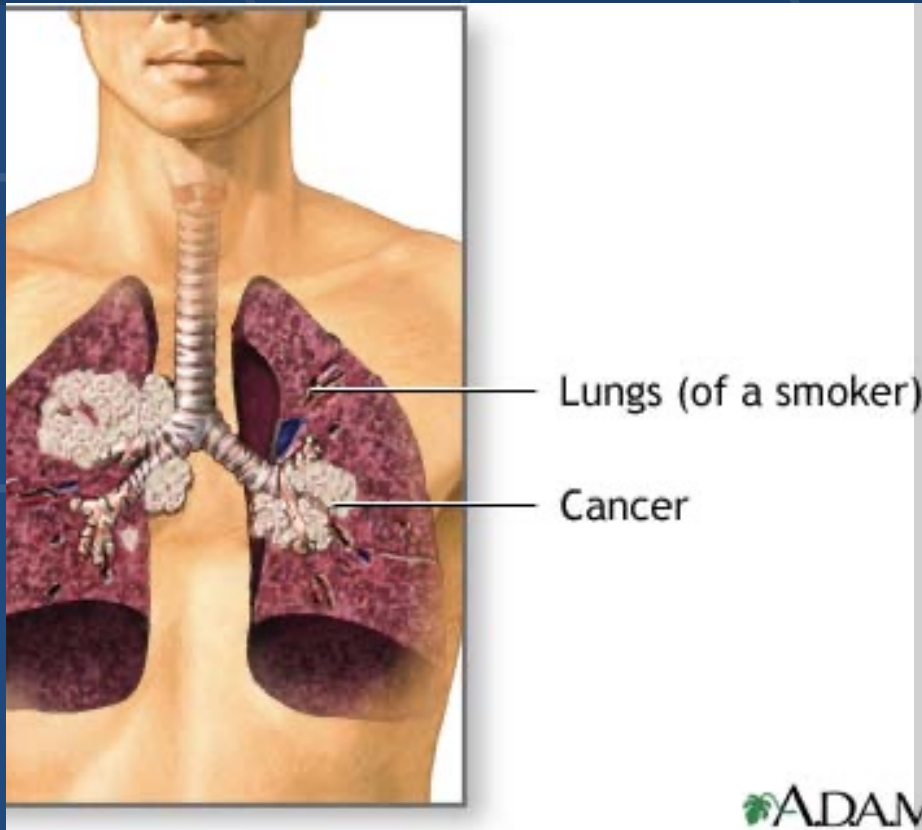
PARANEOPLASTIC CEREBELLAR DEGENERATION

This disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting.

A few days or weeks later, dysarthria, gait and limb ataxia, and variable dysphagia can appear.



PARANEOPLASTIC CEREBELLAR DEGENERATION



The tumors more frequently involved are SCLC, cancer of the breast and ovary, and Hodgkin's lymphoma.

occult neoplasm???

- depends on the clinical circumstances;
- abnormal findings in the medical history and physical examination and not through an extensive blind search;

The weight of evidence argues against performing expensive, invasive, and nondirected tumor searches.

occult neoplasm???

A complete annual physical examination with pelvic, breast (mammogram, if indicated), and rectal examinations (with colonoscopy according to age and family history); urinalysis; complete blood count; blood chemistry tests; and a chest film should suffice in most cases.



Thank you!