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36.1 Overview

- Paraneoplastic disorders of the central nervous system (CNS) are inflammatory disorders affecting various parts of the brain and spinal cord in the setting of a peripheral cancer.
- Ganglia, the peripheral nervous system, the retina, and the neuromuscular junction may also be involved.
- These syndromes appear to represent a group of autoimmune disorders in which antibodies mounted against peripheral cancers target antigens normally expressed within cells (particularly neurons) of the nervous system (i.e., onconeural antibodies).
- The paraneoplastic disorders of CNS fall into a few main categories:
 - Paraneoplastic encephalomyelitis (PEM), with subcategories based on localization:
 - Limbic encephalitis
 - Brainstem encephalitis
 - Cerebellar encephalitis
 - Myelitis
 - Paraneoplastic cerebellar degeneration (PCD)
 - Opsoclonus-myoclonus-ataxia syndrome (OMA)
- These syndromes may also occur in the presence of infiltration of the nervous system by tumor cells or as adverse effects of cancer therapy. In addition, onconeural antibodies (often with accompanying CNS clinical manifestations) may arise in the absence of demonstrable neoplasm.

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36.2 Clinical Features

- All of these disorders may present in children, though they are more frequently encountered in adults in association with lung, breast, or gynecologic malignancies.
- In the pediatric age group, PEM most often accompanies neuroblastoma or rhabdomyosarcoma.
- PCD may be seen with Hodgkin's lymphoma.
- OMA may occur with neuroblastoma.
- Often these syndromes will precede a diagnosis of cancer by weeks to months.
- Symptoms and signs reflect different patterns of CNS involvement:
 - Limbic encephalitis: short-term memory loss, seizures, confusion, psychosis
 - Myelitis: pain, numbness, loss of proprioception
 - OMA: eye movement disturbance, myoclonus ("dancing eyes and dancing feet"), ataxia, and sometimes developmental retardation. Unlike the other paraneoplastic disorders, OMA may have a relapsing-remitting course.
 - Cerebellar degeneration (PCD): ataxia, truncal and hemispheric cerebellar dysfunction

36.3 Neuroimaging

- MR imaging in limbic encephalitis typically demonstrates hyperintense areas within limbic structures on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. Contrast enhancement is not a feature.
- MR images may be normal in PCD, though edema or atrophy may be seen in some cases.
- MR imaging is also frequently normal in OMA, though pontine tegmental abnormalities and cerebellar atrophy have been reported.

- Fluorodeoxyglucose-PET (FDG-PET) may be useful in confirming the presence of an occult neoplasm when conventional CT and MR imaging fail to detect a lesion. FDG-PET sometimes may reveal areas of increased uptake within the CNS itself, correlating with the inflammatory process.

36.4 Pathology

- *Gross pathology*
 - With the exception of mild cerebellar cortical atrophy detectable in some cases of PCD, gross examination is typically unremarkable.
- *Cytology findings*
 - Cerebrospinal fluid (CSF) samples often show a cellular pleocytosis; additional findings may include elevated protein level and/or oligoclonal bands.
- *Histology*
 - All these disorders share several unifying findings:
 - Neuronal loss
 - Astrocytosis (gliosis)
 - Microglial proliferation, often with microglial nodule formation or active neuronophagia
 - Perivascular chronic inflammatory infiltrate of lymphocytes (mainly T cells) and occasional plasma cells (Fig. 36.1A–E)
 - Gray matter is predominantly involved, though there may be secondary white matter loss; leptomeningitis is frequently present.
 - In limbic encephalitis, neuronal loss or inflammation is localized in the medial temporal and inferior frontal lobes, insular cortex, and cingulate gyrus.
 - Brainstem encephalitis mainly involves the medulla.
 - Cerebellar encephalitis of PEM involves neuronal loss in deep structures and nuclei of the cerebellum, with sparing of cortex.
 - PCD involves severe loss of Purkinje cells with accompanying Bergman gliosis; cortex is involved.
 - In myelitis, neuronal loss or inflammation may diffusely involve most of the spinal cord or may be more localized to a few segments.
 - OMA is not characterized by any specific pathologic feature. Approximately half of patients show loss of Purkinje cells, and often there is neuronal loss and inflammation within the brainstem, though localization is variable.
 - Ganglioneuronopathy with dorsal root ganglion cell loss or inflammation and dorsal column degeneration may accompany PEM (Fig. 36.1F).

36.5 Immunohistochemistry

- CD68 will highlight microglia (Fig. 36.2A), whereas T-cell and B-cell markers (CD3 and CD20 respectively) decorate the perivascular lymphoid infiltrates.
- Glial fibrillary acidic protein (GFAP) highlights numerous reactive astrocytes (Fig. 36.2B).
- Immunohistochemical assessment for various viral agents, as well as routine stains for spirochetes (Warthin-Starry stain) or fungal organisms (Gomori methenamine silver [GMS] stain) may be helpful in ruling out various infectious encephalitides.

36.6 Electron Microscopy

- Electron microscopy serves no significant role in the direct diagnosis of paraneoplastic CNS disorders.
- It may, however, be useful in identifying some microorganisms that cause infectious encephalitis that may otherwise closely mimic the histologic features of paraneoplastic disorders, such as microgliosis and perivascular chronic inflammation.

36.7 Differential Diagnosis

- The histologic features of these paraneoplastic CNS disorders may closely mimic infectious (particularly viral or rickettsial) encephalomyelitis. Careful histologic inspection for viral cytopathic effect, use of immunohistochemical stains, tissue culture, and genetic or polymerase chain reaction (PCR) analysis to detect viral or rickettsial genetic material are helpful adjuncts to diagnosis in ruling out infectious etiologies.
- The detection of specific antineuronal antibodies in the serum and/or CSF may serve as a diagnostic tool that directs the search for the tumor to a specific organ system.
 - Anti-Tr can be detected in the CSF of some children with PCD arising in the setting of Hodgkin's lymphoma.
 - Autoantibodies of the IgG3 subclass have been found in pediatric patients with OMA in the setting of neuroblastoma. Anti-Ri has been identified in some.
 - Elevated serum concentrations of chemokines CCL22, CCL17, and CCL21 have been detected in cases of pediatric OMA; CCL21 and CCL22 may serve as potential candidate biomarkers for adrenocorticotropic hormone (ACTH) or a corticosteroid effect in this setting.

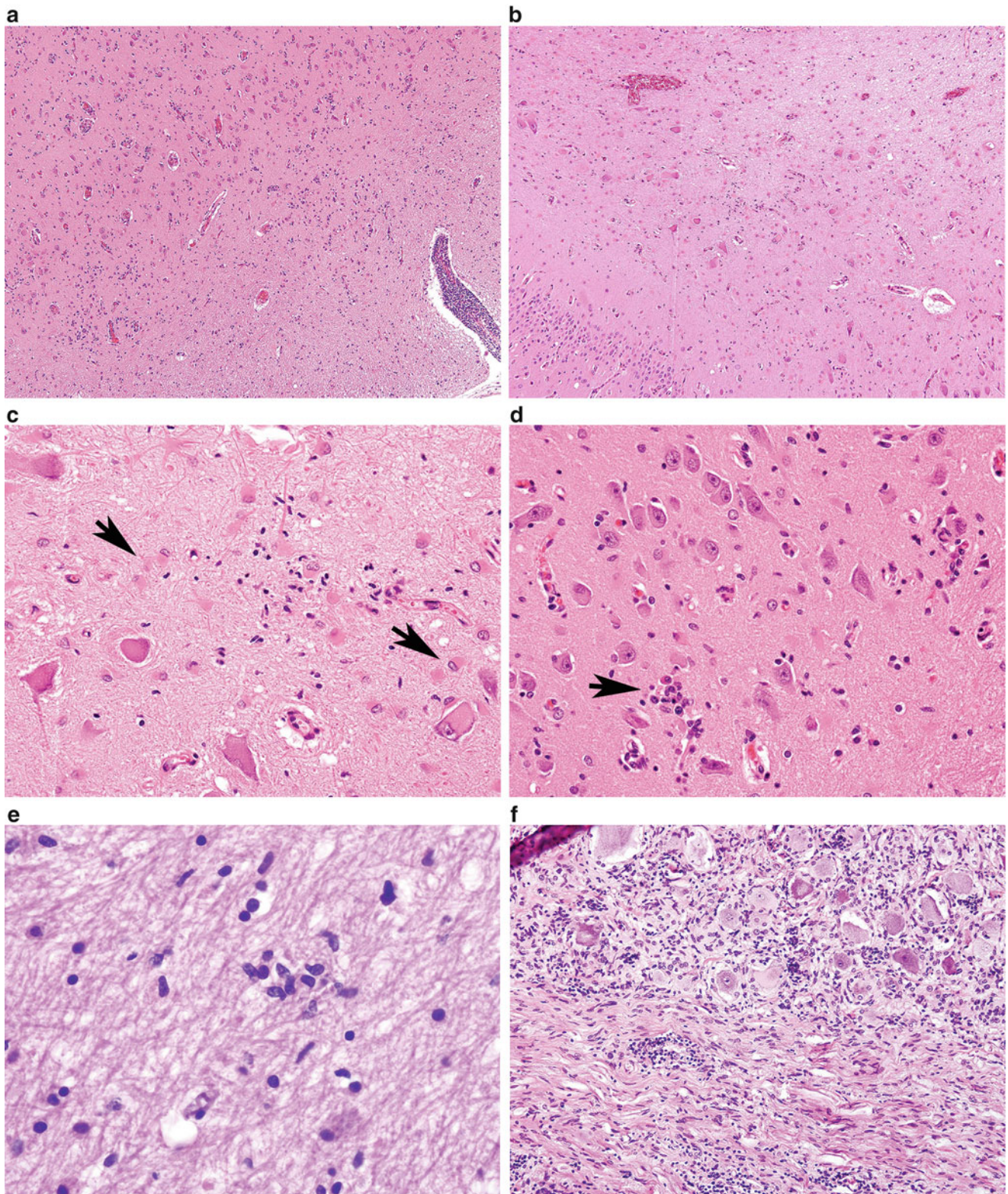


Fig. 36.1 Histologic findings in paraneoplastic CNS disorders. (A) Low-power view of a case of limbic encephalitis, showing perivascular inflammatory infiltrate and increased cellularity within the gray matter, with some cell clustering. (B) This area shows extensive reactive astrocytosis with accompanying neuronal loss in the hippocampal neurons. (C) Examination at higher magnification confirms the presence of numerous reactive astrocytes with brightly eosinophilic cytoplasmic

“bellies” and elongated processes (*arrows*), together with a microglial proliferation. (Note hyperchromatic, rod-shaped nuclei towards the center of the field.) (D) Active neuronophagia is apparent (*arrow*). (E) Microglial nodules may also be seen. (F) This example of paraneoplastic ganglionitis shows the typical lymphocytic inflammatory infiltrate, in some areas surrounding individual ganglion cells. (Courtesy of Dr. Robert Schmidt, Washington University, St Louis, MO)

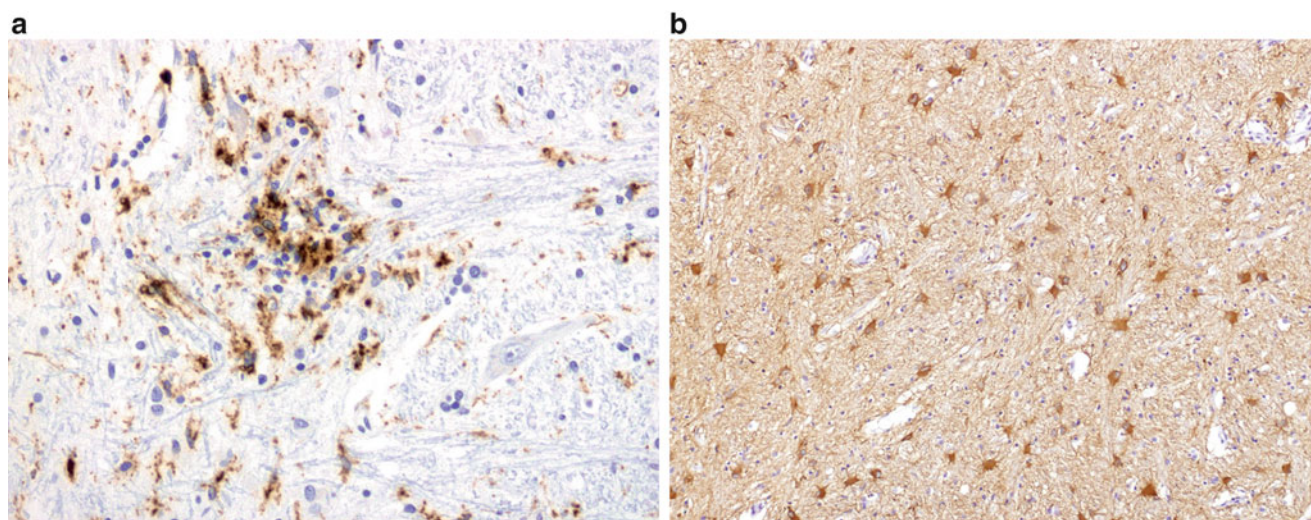


Fig. 36.2 (A) CD68 stain highlights the numerous microglia of these paraneoplastic processes. (B) Glial fibrillary acidic protein (GFAP) decorates the cytoplasm of reactive astrocytes

- Anti-Hu, Ma, and glutamic acid decarboxylase (GAD), and voltage-gated potassium channel (VGKC) antibodies have been found in cases of pediatric limbic encephalitis, though often these cases prove not to be paraneoplastic.

36.8 Prognosis

- In most instances, the most effective treatment for the paraneoplastic CNS disorders is the removal or treatment of the primary peripheral neoplasm, together with immunomodulatory therapies.
- Despite tumor resection and immunosuppressive therapy, some patients with pediatric OMA have poor outcomes that may include developmental and behavioral problems.

Suggested Reading

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