Pseudoneoplasms occur in every organ system. Awareness of them cannot be overstressed. The central nervous system (CNS) is at particular risk of diagnostic error; encased in the calvarium, it is only amenable to indirect “gross examination.” Thus, a basic acquaintance with neuroimaging modalities, including computed tomography and magnetic resonance imaging (MRI), is necessary. Even the process of biopsy can be compromised and result in misdiagnoses. Lesion sampling is often nonrepresentative, and biopsies, particularly stereotaxy specimens, may be minute.

Here, we discuss an assortment of pseudoneoplasms of the nervous system that are easily misinterpreted as tumor in the absence of available clinical and neuroimaging data.

INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumor, a term synonymous with plasma cell granuloma and lymphoid hyperplasia, is a chronic inflammatory lesion of uncertain etiology that more often affects the central than the peripheral nervous system. Inflammatory myofibroblastic tumor, once also considered an inflammatory pseudotumor, is now known to be a neoplasm featuring anaplastic lymphoma kinase overexpression and/or a 2p23 gene rearrangement.1

Inflammatory pseudotumors of the CNS are usually dura-based but can be found anywhere in the neuraxis, including brain parenchyma, spinal cord, choroid plexus, and the pineal region.3 They affect patients of all ages and present on neuroimaging as contrast-enhancing masses resembling tumor (Figure 1, A). Localized involvement of cranial4,5 and spinal6 nerves (Figure 1, C and D) has also been reported.

Grossly, inflammatory pseudotumors vary from soft and gray to firm and white, depending on the relative proportions of inflammatory cells and collagenous stroma. Histologically, they appear similar, regardless of their site of occurrence. The inflammatory infiltrate typically consists of an admixture of lymphocytes, mature plasma cells, and macrophages (Figure 1, B). The lymphocytes often exhibit plasmacytoid features replete with Russell bodies. In some cases, germinal center formation is conspicuous. Collagenization varies in degree, with some lesions being extensively hyalinized. Multinucleate giant cells may be seen in small number but are unassociated with granulomas. The immunophenotype of the lymphocytes is that of a mixed population of T cells and, to a lesser extent, B cells. Although anaplastic lymphoma kinase expression has been reported in intracranial examples,3,7 more recent studies with stringent diagnostic criteria indicate that inflammatory pseudotumors lack anaplastic lymphoma kinase expression, with such expression being a feature of inflammatory myofibroblastic tumor instead.1 Inflammatory pseudotumors may recur, particularly after partial resection. Their overall recurrence rate is approximately 40%.7

Given the contrast-enhancing and sometimes multifocal pattern of CNS involvement by inflammatory pseudotumor, the differential diagnosis is broad. It includes infections as well as neoplasms, such as lymphoma, posttransplantation lymphoproliferative disorder, meningioma, and metastases. Infectious process can often be ruled out with appropriate microbiologic, histochemical, and immunostain studies for organisms. With regard to lymphoma—either parenchymal, deep-seated, and often multifocal (primary lymphoma), or else dura-based (secondary lym-
phoma, mucosa-associated lymphoid tissue lymphoma)—immunohistochemical and molecular genetic studies are indispensable in instances confirming the diagnosis. In cases of posttransplantation lymphoproliferative disorder, a clinical history of organ transplant and/or demonstration of Epstein-Barr virus genome by in situ hybridization aid the diagnosis. Lymphoplasmacyte-rich menigioma, a poorly understood variant, may be difficult to exclude. Careful microscopic examination is required to identify the admixture of meningothelial cells that characterize this lesion. The very existence of lymphoplasmacyte-rich meningioma has been questioned by some, in that (1) reactive meningothelial nest can be encountered in inflammatory processes affecting the dura, and (2) the behavior of some examples of this meningioma variant more closely resembles that of an inflammatory process then a neoplasm.\textsuperscript{8,9} With respect to metastases, attention to the clinical history, ancillary physical findings and, of course, immunohistochemical analysis is required to confirm or refute the diagnosis.

TUMEFACTIVE DEMYELINATION

Multiple sclerosis, a relatively common disease generally affecting young adult women, affects mainly the white matter but may involve gray matter in so-called leukocortical (white and gray matter) disease affecting basal ganglia and/or cortical perivascular regions.\textsuperscript{10} The clinical presentation of demyelinating disease varies greatly, depending on lesion location. Symptoms include aphasia, apraxia, dysesthesia, cognitive abnormalities, and occasionally even headache or seizures. In classic demyelinating disease, MRI findings include multiple, well-demarcated, peripherally contrast-enhancing, round to ovoid or “lobster claw–shaped” subcortical lesions lacking mass effect. In fortuitous images, a distinct perpendicular, perivenous pattern of disease emanates from the lateral ventricles.\textsuperscript{11,12} In some instances, demyelinating disease features atypical imaging characteristics that mimic neoplasia. These include large, solitary lesions associated with mass effect and edema (Figure 2, A). A butterfly configuration mimicking glioblastoma in crossing the corpus callosum is far less commonly seen.\textsuperscript{13–15} Collectively, the features of such “tumefactive demyelination” mimic those of high-grade infiltrative glioma. In such lesions, contrast enhancement may be uniform throughout the lesion, ringlike (complete ring, open ring toward gray matter, or in-

Figure 1. Inflammatory pseudotumor. This T1-weighted, postcontrast magnetic resonance image shows the lesion to involve the skull base bilaterally. It is dura based and contrast enhancing, thus readily mimicking meningioma, metastasis, and lymphoma (A). Microscopically, such inflammatory pseudotumors feature dense lymphoplasmacytic infiltration (B; hematoxylin-eosin, original magnification ×100). Peripheral nerve examples (C) show the process to be largely interfascicular, but minor intratascicular lymphoplasmacytic infiltrates (D) may also be seen (hematoxylin-eosin, original magnification ×100).
Tumefactive multiple sclerosis. It presents as a large, single lesion with peripheral contrast enhancement and mass effect (A). This example was misinterpreted as high-grade glioma. Extensive “tumor debulking” was undertaken. Microscopically, intimate mixture of macrophages and reactive astrocytes was noted (B). Rare perivascular lymphocytes can also be seen (hematoxylin-eosin, original magnification ×200).

Progressive multifocal leukoencephalopathy. Solitary and hyperintense lesions are occasionally encountered and can be mistaken for glioma (A). White matter is affected (B). Nuclear atypia can be prominent (C), but a careful search for nuclear viral inclusions in oligodendrocytes (D) aids in establishing the correct diagnosis (hematoxylin-eosin, original magnifications ×400 [C and D]).

Tumefactive demyelinating disease associated with such misleading imaging findings obviously represents a diagnostic trap. Hypercellularity, somewhat pleomorphic astrocytes with variable nuclear atypia, and abundant macrophages (Figure 2, B), particularly in suboptimally processed or previously frozen tissues, readily mimic infiltrative glioma. Occasional mitotic figures and, in some instances, focal necrosis all conspire to mislead the unwary. Attention to histologic and immunohistochemical details makes the active, inflammatory, demyelinating nature of the process readily apparent. Microsections show the white matter plaque to consist of macrophages filled with Luxol fast blue/periodic acid–Schiff–positive myelin breakdown products in-

Figure 2. Tumefactive multiple sclerosis. It presents as a large, single lesion with peripheral contrast enhancement and mass effect (A). This example was misinterpreted as high-grade glioma. Extensive “tumor debulking” was undertaken. Microscopically, intimate mixture of macrophages and reactive astrocytes was noted (B). Rare perivascular lymphocytes can also be seen (hematoxylin-eosin, original magnification ×200).

Figure 3. Progressive multifocal leukoencephalopathy. Solitary and hyperintense lesions are occasionally encountered and can be mistaken for glioma (A). White matter is affected (B). Nuclear atypia can be prominent (C), but a careful search for nuclear viral inclusions in oligodendrocytes (D) aids in establishing the correct diagnosis (hematoxylin-eosin, original magnifications ×400 [C and D]).

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timately admixed with reactive multipolar astrocytes, some exhibiting multiple micronucleoli (Creutzfeldt cells). Perivascular spaces filled with such macrophages and lymphocytes and relative axonal loss complete the picture. Necrosis is very uncommon but may be seen in rapidly evolving lesions. Sharp demarcation of the lesion from surrounding intact white matter is a characteristic of demyelinating disease well seen on myelin stains, such as Luxol fast blue/periodic acid-Schiff, which shows loss of myelination, its products being blue in early-phase and red in late-phase disease. Immunostains for CD68 label macrophages and show them to crowd perivascular spaces. Neurofilament protein stains show axons to be largely intact. Glial fibrillary acidic protein immunostains highlight the often evenly spaced reactive astrocytes and their processes. An analysis of 168 cases of tumefactive demyelination in a 2-center study, including our own, reported a 31% rate of misdiagnosis by referring pathologists. The most common misdiagnosis was low-grade astrocytoma (39%), followed by nondiagnostic biopsy (18%), high-grade astrocytoma (15%) and, less frequently, oligodendroglioma, infarction, infection, or lymphoma. Simple details aid in the distinction of low-grade astrocytoma (with unapparent cytoplasm and with secondary structures, including subpial and subependymal tumor cell accumulation and perineuronal and perivascular satellitosis, intact parenchyma, lack of macrophages, nuclear atypia, and lymphocytes); high-grade astrocytomas (nuclear atypia, mitoses, secondary structures, endothelial proliferation, palisading necrosis); oligodendroglioma (clear rather than vacuolated cytoplasm, cortical involvement, secondary structures); infarction (necrosis, “red-dead neurons,” microvascular proliferation); infection (viral inclusions, microglial clusters, bacteria and macroabscesses, fungal organisms, granulomas, mycobacteria in macrophages, granulomas); and lymphoma (cytologic atypia/malignancy, B-cell dominance). Obviously, it is of utmost importance to distinguish neoplasm from tumefactive demyelination, because radiotherapy exacerbates inflammatory demyelinating disease. Of essence for the pathologist is an ample biopsy including perilesional parenchyma, one free of frozen section artifacts. Thus, we strongly recommend the use of smear preparations, which aid in identification of cell type by conventional cytologic criteria. Needless to say, awareness of the clinical and neuroimaging data is mandatory.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is the only viral demyelinating process in men. It is confined to the CNS. Most patients are immunocompromised, with human immunodeficiency virus infection being the principal predisposing factor. Other settings include organ transplantation, chronic steroid or immunosuppressive treatment and, of course, hematopoietic malignancy. Only rare cases affect immunocompetent patients. The causative agent is the JC virus, a polyoma virus of the Papoviridae family. The presentation and neurologic findings vary depending on lesion distribution, which is usually multifocal on MRI scan. On T1-weighted images, the lesions are hypointense; although contrast enhancement is typically lacking, fluid attenuated inversion recovery hyperintensity is characteristically seen. Involvement is usually bilateral and multifocal but can become confluent with progression. Only on occasion is a single large lesion encountered (Figure 3, A). In either case, a diagnosis of low-grade infiltrating glioma may be suspected. As in conventional demyelinating disease, lesions typically affect white matter (Figure 3, B). Histologically, they exhibit all the features of demyelination, albeit with less chronic inflammation except in a setting of human immunodeficiency virus–positive patients with highly active antiretroviral therapy. Oligodendrogial cells are primary targets of the virus and exhibit nuclear enlargement with cytopathic effect, specifically a purple, ground-glass appearance (Figure 3, D). In addition, infected astrocytes often possess bizarre, hyperchromatic nuclei (Figure 3, C). Macrophages are somewhat less numerous than are seen in conventional demyelinating disease (multiple sclerosis) or in organizing infarction. The diagnosis can be confirmed by in situ hybridization for JC virus genome, which is demonstrable in oligodendrocytes and, to a lesser extent, astrocytes, as well as by the ultrastructural finding of the organism in the form of filaments and spheres (“spaghetti and meatballs”) within their nuclei. 13

Given the finding of occasional large confluent lesion(s) appearing as a single focus on MRI and the pleomorphic and nuclear atypia of the virus-affected cells, progressive multifocal leukoencephalopathy can easily be mistaken for glioma; namely, astrocytoma or oligoastrocytoma. Strong p53 immunoreactivity of affected glial cells furthers the confusion. Awareness of a clinical history of immune system compromise and of neuroimaging findings, as well as recognition of the numerous macrophages within the lesion and of viral cytopathic effects in glial cells, should resolve the issue.

RADIONECROSIS

For practical purposes, complications of craniospinal irradiation include delayed radionecrosis and leukoencephalopathy. The latter represents diffuse white matter injury, with its resultant degeneration and accompanying intellectual decline, as well as hydrocephalus ex vacuo. 19,20 Acute phase changes, essentially capillary injury and hemorrhage, rarely come to the pathologist’s attention. Here, we will focus on delayed radionecrosis, an uncommon complication of modern-era radiation therapy. In its classic form, it occurs after conventional radiotherapy (total dose >50 Gy) for tumors in the head and neck region. Clinically and on neuroimaging, it often presents dramatically as a contrast-enhancing mass with surrounding edema, an appearance mimicking high-grade glioma. 21-23 Radionecrosis preferentially affects white matter but may extend into the deep cortex. On a limited biopsy, the finding of coagulation necrosis, variable atypia of reactive astrocytes, and prominence of endothelial cells may prompt a misdiagnosis of glioblastoma. A number of clues aid in arriving at the correct interpretation. Foremost is awareness of a prior history of irradiation for extracranial malignancy. The latency period ranges from 1 month to several years and is both dose and time dependent. 24 Radiologically, the contrast-enhancing rim of radionecrosis is often narrower and more uniform than that seen in glioblastoma (Figure 4, A). Furthermore, its outer aspect often follows the undulating contours of the gray matter–white matter junction. On positron emission tomography, radionecrosis is “cold,” or hypometabolic, whereas primary or recurrent glial neoplasms are “hot,” or hypermetabolic. In late stage, radionecrosis generally undergoes dystrophic calcification. Best seen on computed tomogra-
Figure 4. **Radionecrosis.** Presenting as a single lesion with peripheral ring enhancement on magnetic resonance imaging scan (A), the lesion can be mistaken for tumor, as was the case for this patient, who received radiation therapy for poorly differentiated squamous cell carcinoma of the right maxillary sinus. Histologically, large areas of tissue necrosis showing gradual transition to normal parenchyma (B) are seen, as is reactive gliosis, fibrinoid necrosis, and hyalinization of vessels (C; hematoxylin-eosin, original magnifications ×200 [B] and ×400 [C]). Grossly, radionecrosis affects primarily white matter and is often yellow-gray and tissue destructive (D).

Physiologically, the dense deposits appear in deep white matter or as small foci along the gray matter–white matter junction. Grossly, the white matter appears demarcated from relatively intact gray matter. Gray-yellow and granular to mealy, the lesion may, with time, show cavitation and/or superimposed hemorrhage (Figure 4, D). Microscopically, small areas of parenchymal necrosis centered on vessels merge to form expanses of necrotic white matter. Deep cortical layers may also be involved. Radionecrosis typically lacks the neutrophil and macrophage responses that characterize acute infarction and active demyelination, respectively. Plump, gemistocytic-appearing reactive astrocytes are often conspicuous. Unlike in high-grade gliomas, radionecrosis shows gradual transition to more normal white matter and lacks palisading (Figure 4, B). Furthermore, the vascular alteration typically consists of fibrinoid necrosis, hyalinization, and thrombosis (Figure 4, C); not surprisingly, such vessels are prone to hemorrhage. Glomeruloid or ectatic vessels are later-phase findings. Accumulations of necrotic macrophages, once active in early-phase disease, lie trapped and unable to traverse vessels and return to the vasculature. As noted above, calcification may also be seen in the form of amorphous deposits.

The principal differential diagnosis of radionecrosis is a high-grade glioma, specifically glioblastoma. The latter features crowded, cytologically malignant cells with often large hyperchromatic nuclei, increased nuclear to cytoplasmic ratios, and brisk mitotic activity. The presence of palisaded necrosis and endothelial proliferation confirms the diagnosis, as do high MIB-1 labeling indices; labeling in radionecrosis is largely limited to viable macrophages.

**CORTICAL DYSPLASIA**

Cortical dysplasia, an often epileptogenic lesion, consists of a focal or diffuse abnormality of the cerebral cortex and often involves underlying white matter. Symptoms usually present in children and young adults. On MRI, the lesion thickens the cortex, blurs the junction of the gray and white matter, and may taper toward the ventricle (Figure 5, A). As a rule, T2 hyperintensity is seen, but contrast enhancement is not. The microscopic abnormality varies from subtle to remarkable. Architectural disarray of...
the cortex is the key feature. The most widely accepted classification of cortical dysplasia divides it into types I and II, each in turn having 2 subgroups.27 Cortical dysplasia type I is usually cortical in distribution and is devoid of dysmorphic neurons or balloon cells; whereas cortical dysplasia type II affects gray and white matter and contains both dysmorphic neurons and balloon cells. The latter are large cells with abundant glassy cytoplasm (Figure 5, B). Of those, some appear neuronal, featuring small amounts of Nissl substance, somewhat centrally placed nuclei, a prominent nucleolus, apical dendrites pointing to the cortical surface, and positivity for synaptophysin, neurofilament protein, and Neu-N. Yet, others exhibit astrocytic features, such as an eccentric nucleus, prominent processes, and glial fibrillary acidic protein positivity. These cells are usually accompanied by gliosis in both gray and white matter, as well as by loss of myelin in the latter (Figure 5, C). A conspicuous feature in the setting of long-term seizures is dense subpial gliosis. Interestingly, cortical dysplasia can be mistaken for neoplasia; namely, ganglioglioma and infiltrative astrocytoma. Ganglioglioma often presents radiologically as a mural nodule within a cyst and exhibits several helpful diagnostic features, including higher cellularity, dysmorphic or binucleate neurons unassociated with pink cells, pilocytic morphology of the glial component, calcospherites, desmoplasia, and perivascular lymphocytic infiltrates.

**CALCIFIED PSEUDONEOPLASM OF THE NEURAXIS**

Calcified pseudoneoplasm of the neuraxis (CPN) is a highly distinctive lesion of indeterminate nature. Intracranial examples often involve the leptomeninges (Figure 6, B), in which they often lie nestled within a sulcus (Figure 6, A). Spinal examples generally involve paraspinal meninges, soft tissue, and bone. Interestingly, the tissue reaction comprising CPN is not restricted to the neuraxis. It has also been encountered at a variety of sites, including pleura,29 breast,30 and mediastinum.31 Most examples are sporadic, but CNS examples may occur in association with meningioangiomatosis in patients with neurofibromatosis type 2 (see below).32 Radiologically, the lesions are densely...
calcified and appear extra-axial. At the microscopic level, they consist of multiple localized or coalescent, densely calcified, and basophilic nodules featuring a peripheral rim of somewhat radially arranged cells (Figure 6, C). The cells are polygonal to elongated with plump examples being prone to exhibit epithelial membrane antigen immunopositivity. Mitotic figures are rare at best. A characteristic radial pattern of collagen disposition is also noted at the periphery of the nodules. Occasional foreign body giant cells are seen, particularly in osseous lesions.\textsuperscript{33} Osseous metaplasia may be seen. Excision is curative, especially in CNS examples, but may not be possible in large skull base or spinal epidural-osseous lesions secondarily involving vessels and nerves. Significant morbidity and even mortality have been reported in such cases. Local recurrences have been described,\textsuperscript{33,34} but metastases have not.

Once aware of the existence of CPN, its distinctive morphology makes it an easy diagnosis. To the unwary, however, it can be mistaken for other tumors with extensive calcification, including psammomatous meningioma and so-called fibroosseous lesion. Calcifications in meningioma are smaller, round, and lamellated in contrast to the large, irregular calcifications of CPN. Given an association with piloid gliosis and abundance of Rosenthal fibers, even an old, often superficially located pilocytic astrocytoma with abundance of calcifications enters into the differential. Chronic pilocytic gliosis, however, lacks uniform round to oval cells, microcysts, and granular bodies. Spinal lesions may mimic calcified tuberculosis, but CPN, despite nodules of peripheral cellularity and occasional giant cells, does not form granulomas.

**Meningioangiomatosis**

Meningioangiomatosis is a plaquelike, rarely multifocal, nonneoplastic lesion involving the cerebral cortex and, to a varying extent, the leptomeninges. Composed of meningothelial cells and fibroblasts and accompanying vasculature, the process undergoes downgrowth into the cortex (Figure 7, B). It affects both children and young adults and presents with seizures often difficult to control. Although usually sporadic in occurrence, an association with NF2 and meningioma has been described.\textsuperscript{32} When occurring in NF2, meningioangiomatosis is often multifocal and may not be seizure associated.\textsuperscript{35} On MRI, it produces a hypointense T1-weighted signal, is hyperintense on T2, and shows homogenous contrast enhancement (Figure 7, A). On computed tomography scan, leptomeningeal or cortical calcifications may be seen. This is particularly the case when associated with an overlying calcifying pseudoneoplasm of the neuraxis (see above). Microscopically, the cerebral cortex is replaced with small, variably sclerotic vessels accompanied by an admixture of perivascular meningothelial and fibroblast-like cells (Figure 7, C). When the latter predominate, the designation \textsuperscript{36}cellular meningioan-
giomatosis” has been applied, whereas the usual, less cellular form comprises the “vascular” variant.\(^\text{34}\) Islands of entrapped brain parenchyma lie between the vessels and their cellular cuffs (Figure 7, D). Within them, neurons often contain Bielschowsky- or Bodian-positive as well as Tau protein-immunoreactive neurofibrillary tangles.\(^\text{32}\) The subarachnoid space is variably affected but may be expanded by abundant vessels of varying size as well as meningotheelial cells associated with psammomatous calcifications.\(^\text{32}\) As expected, meningotheelial cells are immunopositive for epithelial membrane antigen and fibroblasts for CD34.

The differential diagnoses of meningioangiomatosis includes (1) meningioma, a tumor occasionally arising in transition from meningioangiomatosis;\(^\text{35}\) (2) calcified pseudoneoplasm of the neuraxis, a common accompaniment (see above); and (3) vascular malformation. Meningiomas are solid proliferations of meningotheelial cells and do not exhibit the characteristic perivascular cortical involvement seen in meningioangiomatosis. Furthermore, meningiomas are far less often associated with seizures and tend to occur more often in older adults. Their neuroimaging characteristics do not include cortical extension. Instead, they regularly exhibit a “dural tail sign” corresponding to a wedge-shaped proliferation of tumor and/or vessels at the edges of the tumor–dural interface. Unlike meningioangiomatosis, vascular malformations are composed of vessels more variable in size and are unaccompanied by a cellular component. Nonetheless, vascular malformation enters into consideration because a minority of cases feature large, superficial “feeder vessels.”\(^\text{42}\) In all instances, assessment of the underlying cortex also resolves the issue.

Optimal treatment of meningioangiomatosis consists of simple excisions. A seizure-free outcome is reported in about 45% of cases, although nearly 70% of patients require long-term anticonvulsive therapy.\(^\text{36}\)

**LYMPOCYTIC HYPOPHYSITIS**

Lymphocytic hypophysitis, the most frequent of inflammatory processes affecting the pituitary, characteristically occurs in late pregnancy or shortly after delivery. Males are infrequently affected. Its presentation is nonspecific and includes headache as well as visual field impairment due to chiasmal compression. Hyperprolactinemia is an early finding, whereas pituitary insufficiency involving multiple hormones occurs later in the course. As in the case of pituitary adenoma, diabetes insipidus is rare. On MRI scan, the pituitary may be significantly enlarged, often exhibiting symmetrical suprasellar extension and without deviation of the stalk. With contrast, enhancement is homogenous. Grossly, the specimen is firm and somewhat yellow, thus differing from the soft, gray character of pituitary adenoma. Microscopically, anterior pituitary tissue shows dense infiltration by T lymphocytes and, to a lesser extent, B lymphocytes, as well as plasma cells and small numbers of macrophages (Figure 8). Lymphoid follicles with germinal centers are occasionally present. Fibrosis becomes a dominant feature late in the process. Lymphocytic hypophysitis is an autoimmune process of both cellular and humoral type, as evidenced by predominance of CD8+ T cells\(^\text{40}\) and the presence in serum of antibodies directed against pituitary hormones, most often prolactin\(^\text{40}\)–\(^\text{42}\) or adrenocorticotropic hormone.\(^\text{43}\) Similar inflammatory infiltrates may be seen in other endocrine organs,\(^\text{44}\) including the adrenals,\(^\text{45}\) thyroid,\(^\text{46}\) or parathyroid glands. There may also be a family or personal history of autoimmune disease,\(^\text{47}\) including sarcoidosis,\(^\text{48}\) lupus,\(^\text{49}\) primary biliary cirrhosis,\(^\text{50}\) and retroperitoneal fibrosis.\(^\text{51}\) The most frequently described genetic profiles include human leukocyte antigens DR4 and DR5.\(^\text{51}\) Optimal treatment consists of biopsy or of surgical decompression in cases of visual disturbance resulting from chiasmal compression. Protracted hormone replacement is often necessary. The most important differential diagnosis is pituitary adenoma. Radiographically, the latter often may show asymmetric suprasellar extension and deviation of the pituitary stalk.\(^\text{52}\) Microscopically, adenomas are homogeneous epithelial neoplasms with neuroendocrine features only rarely containing inflammatory infiltrates.\(^\text{54}\)–\(^\text{56}\)

Concurrent adenoma and lymphocytic hypophysitis are also rare.\(^\text{57}\),\(^\text{58}\) Lastly, lymphoma affecting the pituitary is rarely primary at this site, shows no association with pregnancy, and is typically composed of cytologically malignant large B cells.

**PINEAL CYST**

Nonneoplastic glial cysts of microscopic dimension are common (25%–40%) autopsy findings.\(^\text{59}\) When sizable, they are also a frequent (20%) incidental radiologic finding.\(^\text{60}\) Examples reaching a size of several centimeters may also become symptomatic. Such lesions usually occur in young females and present with headache, visual deficits, vomiting, hydrocephalus, and/or Parinaud sign.\(^\text{61}\) Rare examples are associated with sudden death.\(^\text{62}\),\(^\text{63}\) Apoplexy (acute hemorrhage) may occur within pineal cysts.\(^\text{64}\) Radiologically, pineal cysts are well circumscribed, unilocular, and thin walled (Figure 9, A). Residual pineal gland is attenuated and/or displaced posteroinferiorly. Their protein-rich fluid yields a high-signal intensity on proton density and T2-weighted MRI scan.\(^\text{61}\),\(^\text{64}\)–\(^\text{65}\) When accompanied by hemorrhage, the T2-weighted image is dark or may show fluid-fluid levels.\(^\text{64}\) Contrast enhancement is occasionally observed.\(^\text{65}\),\(^\text{66}\) Grossly, covered by the outer layer of leptomeningeal connective tissue as well as by attenuated pineal parenchyma, the cyst wall varies somewhat in thickness. It is filled with yellow fluid and has a smooth, cinnamon-colored inner surface. Microscopically, its wall is composed of hypocellular, compact and fibrillated astrocytic tissue containing small numbers of Rosenthal fibers (Figure 9, B and C). Hemosiderin-containing macrophages are also common. Adjacent pineal parenchyma is relatively demarcated from this glial tissue. It retains its vague lobularity and frequently shows conchoid calcifications (corpora arenacea) but is compressed and often loses some of its normal lobular architecture (Figure 9, B). As a result, residual pineal tissue may be misinterpreted as pineal parenchymal tumor; namely, pineocytoma or pineal parenchymal tumor of intermediate differentiation. Glial fibrillary acidic protein immunostains highlight the piloid astrocytes comprising the cyst wall; NF protein immunostain reveals complete absence of axons within this tissue. The prognosis of symptomatic pineal cyst is excellent; its complete resection, in addition to the pineal gland, is curative.

The two most common diagnostic errors surrounding pineal cyst are pilocytic astrocytoma and pineocytoma. Both misdiagnoses are made more likely when the cysts are cut en face, apparently increasing their areas. It is for this reason that the cysts should be fixed prior to gross
Figure 9. Pineal cyst. A, This characteristic example forms a uniloculate mass in the pineal and posterior third ventricular region. B, The cyst wall contains astrocytic tissue and compressed residual pineal parenchyma at its periphery (hematoxylin-eosin, original magnification ×200). C, The glial component exhibits mild atypia (hematoxylin-eosin, original magnification ×400). D, For comparison, normal pineal gland parenchyma is also illustrated (hematoxylin-eosin, original magnification ×200).

Figure 10. Localized hypertrophic neuropathy. A, The process involves several fascicles (hematoxylin-eosin, original magnification ×40). B, Note characteristic, well-spaced, true onion bulbs (Schwann cells) in a hypocellular matrix (hematoxylin-eosin, original magnification ×400).

cutting. It is the radiographic description of a cyst coupled with the finding of Rosenthal fibers and/or eosinophilic granular bodies that prompts the astrocytoma diagnosis. Pineal cyst lacks the enhancement of pilocytic astrocytoma. In addition, is unilocular and lacks microcysts as well as glomeruloid vessels. Lastly, whereas NF protein immunostains show the presence of at least some axons within the substance of pilocytic astrocytoma, the glial lining of a pineal cyst is devoid of axons. A pineocytoma misdiagnosis occurs when the attenuated pineal tissue is (1) compressed and its lobular architecture effaced, or (2) when it appears to be abundant in maloriented specimens. Helpful features differentiating pineal cyst from pineocytoma include lack of pineocytomatous rosettes and the presence of both corpora arenacea and sharp demarcation from cyst lining in the pineal cyst. Intermediate tumors
## Pseudoneoplasms: Clinicopathologic Features and Differential Diagnoses

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<td>Oligodendrocytes with viral cytopathic effect</td>
<td>Myelin stains (LFB-PAS)&lt;sup&gt;+&lt;/sup&gt;, CD68&lt;sup&gt;+&lt;/sup&gt;, JC virus ISH&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Astrocytoma, Oligoastrocytoma</td>
</tr>
<tr>
<td><strong>Radionecrosis</strong>&lt;br&gt;History of head and neck irradiation</td>
<td>Enhancing lesion with edema and mass effect</td>
<td>Coagulative necrosis; vascular fibrin impregnation, thrombosis and hyalinization; absence of neutrophilic and viable macrophage response</td>
<td>GFAP&lt;sup&gt;+&lt;/sup&gt; (reactive astrocytes), NF protein negative, Myelin stain (LFB-PAS)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Astrocytoma, Infarction</td>
</tr>
<tr>
<td><strong>Cortical Dysplasia</strong>&lt;br&gt;Seizure association in young patients</td>
<td>MRI: thickened cortex and subcortical T2 hyperintensity</td>
<td>Loss of cortical layers; large pink cells, abnormal neurons, bizarre astrocytes</td>
<td>NF/synaptophysin positive or negative, GFAP positive or negative, MIB-1&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Ganglion cell tumor, Infiltrative astrocytoma</td>
</tr>
<tr>
<td><strong>Calcified Pseudoneoplasm of the Neuraxis</strong>&lt;br&gt;Leptomeningeal or destructive spinal lesion</td>
<td>Densely calcified intracranial, leptomeningeal mass with or without handlike cortical abnormality; destructive spinal mass</td>
<td>Densely calcified nodules with radial fibrillarity and cellular periphery</td>
<td>EMA&lt;sup&gt;+&lt;/sup&gt;, Psammomatous meningioma, Pilocytic astrocytoma, Meningioangiomatosis</td>
<td></td>
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<tr>
<td><strong>Meningioangiomatosis</strong>&lt;br&gt;Adolescent with uncontrollable seizures</td>
<td>Contrast-enhancing, bandlike cortical lesion with or without calcification</td>
<td>Cortical hypertangularity with meningotheial cells and fibroblasts; occasional neurofibrillary tangles</td>
<td>EMA&lt;sup&gt;+&lt;/sup&gt;, CD34&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Meningioma, Vascular malformation</td>
</tr>
<tr>
<td><strong>Lymphocytic Hypophysitis</strong>&lt;br&gt;Late pregnancy/postpartum presentation</td>
<td>Homogenously enhancing pituitary mass with symmetric suprasellar extension with or without “dural tail”</td>
<td>Lymphocytes, Plasma cells, Macrophages, Collagen</td>
<td>CD3, CD4, CD8, CD68&lt;sup&gt;+&lt;/sup&gt;, CD38&lt;sup&gt;+&lt;/sup&gt;, CD20&lt;sup&gt;+&lt;/sup&gt; (minor)</td>
<td>Pituitary adenoma, Lymphoma, Langerhans cell histiocytosis, Germinoma</td>
</tr>
<tr>
<td><strong>Pineal Cyst</strong>&lt;br&gt;Often incidental finding in young females with nonspecific symptoms</td>
<td>MRI: Unilocular cyst with high intensity on T2 ± fluid level</td>
<td>Three layers: leptomeninges, distorted pineal parenchyma, hypocellular piloid gliosis; hemosiderin</td>
<td>MIB-1 low throughout, NF in glial wall</td>
<td>Pilocytic astrocytoma, Pineocytoma</td>
</tr>
<tr>
<td><strong>Localized Hypertrophic Neuropathy</strong>&lt;br&gt;Reactive lesion affecting a single nerve</td>
<td>Enhancing, fusiform enlargement of a sizable nerve</td>
<td>True onion bulbs (Schwann cells), Collagen deposition, Mucinous matrix</td>
<td>S&lt;sub&gt;100&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;, NF&lt;sup&gt;+&lt;/sup&gt;, EM&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Intraneural perineuroma, Neurofibroma</td>
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</table>

Abbreviations: ALK, anaplastic lymphoma kinase; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; IHC, immunohistochemical; ISH, in situ hybridization; LFB, Luxol fast blue; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PTLD, posttransplantation lymphoproliferative disorder.
are architecturally solid, lack lobularity entirely, and may show mitotic activity.

LOCALIZED HYPERTROPHIC NEUROPATHY

Localized hypertrophic neuropathy (LN) is a rare lesion usually affecting individual nerves. Its reactive/hyperplastic nature is supported by its occurrence in association with episodes of demyelination and remyelination as well as with chronic inflammatory demyelinating neuropathy67 or polyneuropathies.68 The lesion is unassociated with a known syndrome, particularly NFI. It may affect both cranial9,70 and spinal71,72 nerves. These show fusiform expansion and may measure up to 15 cm in length.72,73 Reports of the MRI appearance of LHN are few, but post-contrast enhancement may be seen. The diagnostic morphologic feature is “true” onion bulb formation, with individual nerve fibers (axons and their Schwann sheaths) being surrounded by whorls of uniform, cytologically benign Schwann cells encircling variably myelinated axons (Figure 10). Collagen is present within the onion bulbs, and the endoneurium contains an abundant mucinous matrix. Predictably, the Schwann cells are S100 protein immunopositive, and axons are readily seen on neurofilament protein stain. Myelin stains, such as Luxol fast blue, show variable amounts of myelin.

The only differential diagnoses of LHN include intra- neural perineurioma and neurofibroma. Perineurioma similarly affects individual nerves and multiple fascicles. It consists of neoplastic perineurial cells similarly disposed around nerve fibers.74 Termed “pseudo-onion bulbs,” they resemble the whorls in LHN but differ in several respects. Pseudo-onion bulbs (1) are composed of epithelial membrane antigen–positive perineurial cells, (2) occur in varying size, with some being very large and encompassing numerous nerve fibers, and (3) may be bridged by perineurial cells, thus linking adjacent bulbs. Furthermore, the endoneurium of perineurioma lacks an abundant mucinous matrix. Ultrastructural studies show the whorling cells of LHN to possess classic features of Schwann cells, including continuous basal lamina, but few rudimentary junctions. In contrast, the whorling cells of intraneural perineurioma are perineurial, showing numerous surface pinocytic vesicles, discontinuous basal lamina, and frequent tight junctions. The general consensus is that LHN is a nonneoplastic lesion and is not a part of the spectrum of intraneural perineurioma.25 Perineuriomas have been associated with abnormalities of chromosome 22.74 Lastly, neurofibromas, particularly plexiform examples, occasionally feature onion bulb–like arrangements of Schwann cells around overrun axons. Such lesions feature a mucoid matrix but are also much more cellular, with spaces between axons containing Schwann cells, perineurial-like cells, and fibroblasts.

CONCLUSIONS

We have attempted to show that a variety of pseudo- neoplasms affect the central and peripheral nervous system. Their clinical presentation, neuroimaging findings, and/or histology features (Table) can all mimic neoplasia. Maintaining a broad differential diagnosis is essential. Lack of awareness of these lesions precludes their recognition and may result in serious consequences for the patient. Inappropriate treatment may lead to exacerbation of the condition; for example, the neurologic decline of patients with demyelinating disease after having undergone irradiation. Further surgery, thought to be warranted on a misdiagnosis, may also further debilitate a patient.

The identification of tumor mimics may be difficult under the best of circumstances, but it is needlessly complicated by lack of acquaintance with clinical and radiologic data, a minute biopsy, frozen section artifacts, and the tissue waste that accompanies failure to obtain unstained sections from the onset. Obtaining a second, more ample and higher-quality biopsy may best serve the patient in such instances.

References
