Cancer Neurology: Primary CNS Lymphoma, Paraneoplastic Syndromes, and Pituitary Adenoma

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Cover Illustration by Kathryn K. Johnson
INTRODUCTION

This manual is the second of a 2-part review of neuro-oncology. The first part of the review addressed the evaluation and management of patients with primary malignant brain tumors and central nervous system (CNS) metastases. In this part, 3 clinical cases are presented that evolve over the course of the discussion to encompass evaluation and management of primary CNS lymphoma (PCNSL), paraneoplastic syndromes, and pituitary adenomas. These topics frequently appear on board examinations and represent some of the more intriguing entities encountered in neuro-oncology.

PRIMARY CNS LYMPHOMA

EPIDEMIOLOGY AND PATHOGENESIS

Systemic non-Hodgkin’s lymphoma (NHL) may secondarily involve the nervous system in 5% to 10% of patients. PCNSL is an unusual extranodal NHL variant that exclusively involves the nervous system and eyes. Only rarely is there spread to the systemic compartment. PCNSL represents 3.1% of CNS tumors, with approximately 2000 new diagnoses per year in the United States.

In 90% of cases, PCNSL is diagnosed histopathologically as diffuse, large B-cell lymphoma, which is also the most common subtype of systemic NHL (Figure 1). Other subtypes of PCNSL have been described, including very rare T-cell variants. The pathogenesis of PCNSL is perplexing, because lymphatic tissue is not found in the normal brain. Emerging data suggest that PCNSL may develop outside the nervous system and then traffic to the brain by poorly defined mechanisms. Although the cell of origin remains unknown, PCNSL cells frequently express markers associated with the germinal center stage of B-cell differentiation.

RISK FACTORS AND PROGNOSIS

Immunodeficiency is the strongest known risk factor for all subtypes of lymphoma, including PCNSL. The immunocompetent population is infrequently affected; most immunocompetent patients with PCNSL are older adults, and there is a slight male preponderance. Patients with HIV have at least a 1000 times greater risk of developing PCNSL compared with the general population. Other acquired and congenital immunodeficiency states are also risk factors. The Epstein-Barr virus (EBV) plays a critical role in the development of immunodeficiency-associated PCNSL, although a detailed mechanism remains to be established. There are no convincing data to suggest that EBV or any other infectious agent is involved in the pathogenesis of PCNSL in immunocompetent patients.

Although localized extranodal systemic NHL is compatible with long-term survival in 70% or more of patients, PCNSL is universally fatal. Factors that predict decreased survival among patients with PCNSL include age greater than 60 years, impaired performance status, elevated serum lactate dehydrogenase (LDH), increased cerebrospinal fluid (CSF) protein, and involvement of deep brain structures. Depending upon the number of adverse prognostic factors, 2-year survival rates vary between 24% and 85%. Expression of B-cell lymphoma-6 (BCL6), a transcriptional repressor involved in germinal center formation, may be an important marker of favorable prognosis in patients with PCNSL. The precise mechanism by which BCL6 contributes to the pathogenesis of NHL is unknown, but impaired BCL6 expression may prevent normal lymphocyte differentiation. BCL6 and other emerging molecular prognostic markers are the focus of current research efforts.

CLINICAL FEATURES

Case 1 | Presentation

A healthy, 78-year-old woman is referred by her primary care physician to a neurologist for further evaluation. The patient has experienced 2 to 3 months
of slowed movements, mild dysarthria, and decreased energy level. In addition, in recent weeks, her gait has become unsteady and she has had several falls with minor injuries. Examination by the neurologist reveals perseveration, executive dysfunction, difficulty with left-sided rapid alternating movements, a very unsteady gait, and diffuse hyperreflexia with bilateral Babinski signs.

- Is this patient’s presentation consistent with PCNSL?

**Signs and Symptoms of Primary CNS Lymphoma**

The clinical examination findings thus far in this patient are consistent with a subacute, multifocal disease process that involves the brain and possibly spinal cord. Based on the information available, PCNSL is a strong possibility. As is true for all mass lesions in the CNS, the signs and symptoms of PCNSL reflect the portions of the neuraxis that are involved. (For additional information, the reader is referred to the first half of this review, which is available at www.turner-white.com/brm/bneur.htm.)

Unlike patients with systemic NHL who often present with B symptoms (eg, fever, weight loss, night sweats), patients with PCNSL present with neurologic signs and symptoms. Focal deficits and neuropsychiatric problems (eg, apathy, depression, bradyphrenia, encephalopathy) are reported most frequently. Seizures are distinctly uncommon because of the relative rarity of cortical involvement. Patients who complain of floaters, decreased visual acuity, or eye pain may be among the 10% to 20% of immunocompetent patients who have ocular involvement at the time of presentation. In 20% of these cases, patients are asymptomatic, which explains why all patients with newly diagnosed PCNSL must have a careful ophthalmologic examination. Ocular disease may precede the development of more typical intracranial disease, and it may also develop in the setting of recurrence after successful treatment. Cranial nerve palsies are observed in some patients and generally indicate leptomeningeal infiltration. As many as 40% of patients may have leptomeningeal lymphoma, but symptomatic disease occurs in less than a third of these individuals. The subarachnoid space is a common site of tumor recurrence that must be investigated whenever a patient with PCNSL complains of worrisome neurologic symptoms. Systemic dissemination at recurrence is unusual and occurs in fewer than 15% of patients with advanced disease.

**EVALUATION FOR PRIMARY CNS LYMPHOMA**

**Case 1 Continued**

The patient undergoes gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, which reveals extensive bilateral T2-hyperintense enhancing lesions involving deep gray and subcortical white matter. The patient is subsequently admitted to the hospital for further evaluation.

- What diagnostic tests should be obtained in the evaluation for PCNSL?

Components of the standard diagnostic and staging evaluation for PCNSL are listed in Table 1.

**Neuroimaging**

Many patients undergo computed tomography (CT) scanning as the first test ordered by a physician, often before the diagnosis is considered. PCNSL lesions are isodense to moderately hyperdense on CT, which is thought to reflect their dense cellularity and high nuclear-to-cytoplasmic ratio. Homogeneous contrast enhancement is typical.

When PCNSL is suspected, gadolinium-enhanced MRI of the brain and spinal cord is essential. PCNSL lesions may have variable signal intensity on MRI (Figure 2). Typical findings include T1 hypointensity and T2 hyperintensity. T2 hypointensity is analogous to CT hyperdensity and is sometimes observed in highly hypercellular lesions. Restricted water diffusion as indicated by
Hyperintensity on diffusion-weighted imaging sequences and hypointensity on apparent diffusion coefficient sequences are characteristic but not universal findings. The vast majority of PCNSL lesions enhance homogeneously with contrast. In a series of pretreatment MRI examinations of 100 patients with confirmed PCNSL, only 1 patient had a nonenhancing lesion. Sharp borders between the lesion and normal brain parenchyma are typical. A pattern of enhancement that follows the Virchow-Robin perivascular spaces is highly suggestive of PCNSL but is not often observed. After treatment, loss of contrast enhancement is common. Immunocompromised patients with PCNSL, enhancement is more likely to be heterogeneous or ring-shaped, suggestive of areas of necrosis. Similarly, T2-weighted hyperintensity and CT hypodensity are more often observed in patients with impaired immunity. The radiographic differential diagnosis for PCNSL includes other primary brain tumors, metastases, abscesses, and various infections (Table 2). Although typical MRI features are helpful in distinguishing between these lesions, a histologic diagnosis is usually mandatory before treatment can be initiated.

In most cases, PCNSL presents as 1 or more cerebral lesions that are typically in contact with the CSF. Immunocompetent patients are more likely to have a solitary lesion, whereas immunodeficient patients are equally likely to have a solitary lesion as multiple lesions. Most PCNSL lesions (approximately 85%) are found in the supratentorial compartment, but infratentorial masses, particularly in the cerebellum, are not inconsistent with the diagnosis. Most intracranial lesions develop in proximity to the ventricles and involve thalamus, basal ganglia, periventricular white matter, or corpus callosum. PCNSL and glioblastoma multiforme have a particular predilection for corpus callosum and should always be considered in the differential diagnosis of mass lesions that involve it. Primary leptomeningeal and primary spinal PCNSL are unusual presentations. Leptomeningeal involvement is much more frequently seen in the context of parenchymal brain disease. The primary spinal variant of PCNSL almost always involves intramedullary tumor nodules that produce myelopathy.

**CSF Evaluation**

The CSF evaluation may also be useful diagnostically and should be performed routinely as part of the diagnostic algorithm. It is important to note that lumbar
Puncture cannot be safely performed until the risk of herniation has been assessed with neuroimaging. CSF should be sent for routine studies including protein, glucose, and cell count; cytology and flow cytometry; and immunoglobulin (Ig) heavy chain rearrangement studies in centers where this is available. In immunocompromised patients, polymerase chain reaction (PCR) analysis for EBV DNA is also recommended. In most patients with PCNSL, routine studies are normal or show a mild lymphocytic pleocytosis and moderately elevated protein. Cytology is diagnostic in approximately 25% to 30% of cases.16 Diagnostic yield may be increased by obtaining large-volume, serial CSF samples and flow cytometry. PCR analysis for Ig heavy chain rearrangement is a newer technique that can identify a monoclonal lymphocyte population when other tests are negative; the sensitivity and specificity in the clinical setting are uncertain. In HIV-infected patients, CSF EBV DNA positivity may be adequate to confirm the diagnosis of PCNSL, but some studies suggest that the specificity is too low for the test to be clinically useful.17

Surgery

Except when CSF analysis (or occasionally vitreal biopsy, as discussed below) provides a definitive diagnosis, stereotactic brain biopsy is needed. The role of stereotactic biopsy as the gold standard for diagnosis of PCNSL is well-established, and morbidity rates are low. Because surgical resection of PCNSL lesions provides no benefit, open craniotomy is an option that may provide tissue confirmation of the diagnosis as well, although this is controversial and is not performed in all centers.

Other Diagnostic and Staging Studies

A series of additional investigations should be performed for staging in patients with confirmed PCNSL. CT scanning of the chest, abdomen, and pelvis is important to identify occult systemic disease, which would change the diagnosis to widespread systemic NHL. The distinction is not just one of nomenclature, as the treatment regimens used for PCNSL are inadequate for systemic disease. The converse is also true. When PCNSL is suspected but the diagnosis has yet to be confirmed, body CT scanning may identify systemic disease and provide a source of diagnostic tissue that obviates the need for brain biopsy.

A careful slit-lamp examination is a critical element in the staging evaluation of patients with PCNSL. Ocular involvement manifests as a cellular infiltrate in the vitreous. In patients with ocular disease in whom a CSF evaluation is nondiagnostic, vitreal aspiration or vitrectomy is an option that may provide tissue confirmation of the diagnosis. The establishment of ocular involvement is also important because it may require specific treatment such as globe irradiation. Some experts favor bone marrow biopsy as part of the initial staging evaluation as well, although this is controversial and is not performed in all centers.

In addition to routine blood tests necessary to rule out systemic disease (complete blood count, electrolytes, renal and liver function tests, HIV serology), serum LDH level should be obtained in all patients with PCNSL because of its prognostic significance (see page 2, Risk Factors and Prognosis). Some practitioners recommend routine testicular examination and ultrasonography for men diagnosed with PCNSL. Primary testicular lymphoma is associated with an unusually high rate of nervous system involvement.19

TREATMENT

Case 1 Continued

The patient undergoes MRI of the spine and CT of the body, both with negative results. A slit-lamp examination

Table 2. Differential Diagnosis of Primary CNS Lymphoma on Brain MRI

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Typical Distinguishing Features</th>
</tr>
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<tbody>
<tr>
<td>Neoplasm</td>
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<tr>
<td>High-grade glioma</td>
<td>Heterogeneous enhancement</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Location at gray-white junction</td>
</tr>
<tr>
<td></td>
<td>Extensive surrounding edema</td>
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<tr>
<td></td>
<td>History of systemic cancer</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>History of transient neurologic dysfunction</td>
</tr>
<tr>
<td>(if diffuse white matter involvement)</td>
<td></td>
</tr>
<tr>
<td>Tumefactive demyelinating lesion</td>
<td>Rare homogeneous enhancement</td>
</tr>
<tr>
<td>Paraneoplastic disease (eg, limbic encephalitis)</td>
<td>Rapid symptom onset</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>Ring enhancement</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy*</td>
<td>Minimal or absent enhancement</td>
</tr>
<tr>
<td>Toxoplasmosis*</td>
<td>Ring enhancement</td>
</tr>
</tbody>
</table>

CNS = central nervous system; MRI = magnetic resonance imaging.
*Primarily considered in immunocompromised patients.
shows evidence of vitreal inflammation in the right eye. Visual acuity is slightly decreased in the right eye. CSF examination is nondiagnostic, including cytology, flow cytometry, and PCR analysis for Ig heavy chain rearrangement. CSF protein is 65 mg/dL (upper limit of normal = 45 mg/dL). HIV serology is negative. Results of routine laboratory tests are normal, but serum LDH is elevated at 290 U/L (upper limit of normal = 250 U/L). A repeat CSF sample again reveals elevated protein, and this time cytology is reported as “a few atypical lymphocytes of unclear significance.” Too few cells are present for flow cytometry. PCR analysis for Ig heavy chain rearrangement is once again nondiagnostic. A third CSF sample is diagnostic of B-cell NHL by cytology and flow cytometry.

- What treatment options should be considered for this patient?
- How should the ocular findings be addressed?
- What are the benefits of eliminating WBRT from the treatment plan?

Although PCNSL is among the most radiosensitive and chemosensitive of CNS tumors, the optimal treatment regimen for patients with newly diagnosed PCNSL is unknown. As noted, the only role for surgery in PCNSL management is establishment of a tissue diagnosis.

Radiotherapy

Historically, whole brain radiation therapy (WBRT) was used as initial therapy because of high radiographic response rates. However, subsequent data have shown that remission after WBRT alone is transient, and delayed neurocognitive toxicity is substantial, particularly in older patients. Median survival is in the range of 12 to 18 months.

Chemotherapy

Many chemotherapy regimens have been studied in an attempt to improve upon the poor outcomes associated with WBRT alone. Interestingly, systemic NHL regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have not demonstrated efficacy against PCNSL, perhaps because of poor blood-brain barrier penetration. Methotrexate forms the backbone of most chemotherapy regimens used to treat PCNSL. This antimetabolite chemotherapeutic agent works by interruption of folate metabolism. Blood-brain barrier penetration by methotrexate is limited, so high-dose systemic treatment (2–8 g/m²) is required to achieve cytotoxic levels in the nervous system. This approach may avoid the need for intrathecal chemotherapy, even in patients with leptomeningeal lymphoma. When methotrexate-based chemotherapy is combined with WBRT, 2-year survival is observed in 43% to 73% of patients, and median survival is reported in the range of 30 to 60 months. Other lipophilic drugs often administered in conjunction with methotrexate include cytarabine, procarbazine, and temozolomide. Whether these agents confer additional benefit beyond that provided by methotrexate alone is unknown.

Because of treatment-related neurotoxicity rates as high as 26%, there has been growing interest in methotrexate-based chemotherapy alone without WBRT. Small studies reveal promising results with median overall survival of 4 to 5 years. At present, most centers that care for patients with PCNSL provide methotrexate-based combination chemotherapy regimens with or without WBRT. The use of additional chemotherapeutic agents and intrathecal chemotherapeutics varies from center to center.

Role of Steroids

It is important to note that corticosteroids alone may provoke rapid, dramatic tumor responses in as many as 40% of PCNSL patients. The responses are almost always short-lived, but they can be problematic when they occur prior to definitive diagnosis. Because steroids result in lymphocyte apoptosis, such treatment can dramatically reduce diagnostic yield, regardless of diagnostic modality employed. Even stereotactic biopsy may be nondiagnostic in a patient who has been treated with a single large dose of dexamethasone. Of course, steroid administration may be mandatory in a patient who presents with decreased level of consciousness due to mass effect. In this case, definitive diagnosis may be delayed by weeks or months.

Treatment of Ocular Disease

As for typical PCNSL, the optimal treatment regimen for ocular lymphoma (ie, lymphoma that involves the CNS and eye or the eye alone) is undefined. The disease is sufficiently rare that very few data are available to guide management decisions. Most authorities recommend bilateral ocular radiotherapy (RT) (35- to 40-Gy dose of fractionated irradiation over 5 weeks) followed by a high-dose methotrexate-based chemotherapy regimen. Visual complaints resolve with treatment, but long-term adverse effects can include cataracts, retinal atrophy, optic neuropathy, and rarely, vitreal hemorrhage. Because primary ocular lymphoma (ie, lymphoma that presents initially in the eye without evidence of CNS disease) invariably relapses in the CNS, chemotherapy is generally provided in this circumstance.
Treatment-Associated Neurotoxicity

Available data suggest that WBRT and methotrexate-based chemotherapy act synergistically to produce higher rates of neurotoxicity than either modality alone. In a large series of PCNSL patients treated with various combinations of chemotherapy and WBRT, neurotoxicity developed in 24%. Risk factors for the development of neurotoxicity included age 60 years or older and WBRT. The patients initially complained of inattention, slowness, apathy, and memory difficulties. Over months to years, most patients progressed to meet criteria for dementia. Neuropsychological testing revealed problems with executive function, processing speed, and memory. In conjunction with these cognitive difficulties, a gait disorder emerged and was characterized by small shuffling steps, widened base, difficult turns, and postural instability. Patients ultimately lost the ability to walk altogether. Other manifestations of advanced dementia appeared, including dysphagia, pseudobulbar symptoms, and particularly, incontinence. The patients who did not die of recurrent lymphoma died as a result of progressive dementia. MRI showed atrophy and extensive subcortical white matter hyperintensity on T2-weighted images. Some patients developed ventriculomegaly out of proportion to atrophy and were felt to have normal-pressure hydrocephalus. However, ventriculoperitoneal shunting was not helpful in this cohort. The authors noted that this syndrome of progressive dementia is indistinguishable clinically from that caused by subcortical arteriosclerotic encephalopathy (Binswanger’s disease), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), or normal-pressure hydrocephalus. In the patients who underwent autopsy, findings included gliosis and spongiosis within subcortical white matter. Diffuse demyelination and axon loss were observed, and all patients had evidence of small-vessel vasculopathy. The latter finding suggests that WBRT-induced vascular injury may be an important mediator of neurotoxicity in this patient population.

In light of this information, there is growing interest in developing treatment regimens for PCNSL that rely on chemotherapy alone. Although methotrexate itself invariably produces white matter changes on MRI, rates of neurotoxicity in treated patients are significantly lower. The present challenge is to develop a methotrexate-based chemotherapy regimen that provides long-term disease control.

Case 1 Conclusion

Because the patient is elderly and deemed to be at high risk for treatment-related neurotoxicity, she is treated with high-dose methotrexate in conjunction with RT limited to the eyes. After 2 months of therapy, the patient feels well and has achieved a complete radiographic response. She is treated with methotrexate for 1 year and then enters a period of surveillance. Two years later, she dies of an unrelated myocardial infarction. There is no evidence of residual disease at autopsy, but methotrexate-related leukoencephalopathy is detected.

**PARANEOPLASTIC SYNDROMES**

**EPIEMIOLOGY AND PATHOGENESIS**

Often considered remote effects of cancer on the nervous system, paraneoplastic syndromes are unique among the nonmetastatic complications of cancer (ie, coagulopathy, infection, metabolic and nutritional disorders, side effects of therapy) in that they often develop prior to the diagnosis of cancer, may produce profound disability, and are usually irreversible if not treated early. Various paraneoplastic syndromes have been described that may affect the nervous system at any level, from muscle or sensory organ to cortex (Table 3). The pathophysiology of these syndromes is heterogeneous and incompletely understood, but immunologic mechanisms are felt to be paramount. In many of these disorders, antibodies and T-cell responses have been detected against nervous system antigens. The prevailing theory is that some tumors express antigens that are normally expressed only in the immune-privileged nervous system. This leads to an immune response against the tumor and induces an autoimmune reaction directed against normal structures.

Because these disorders are rare and heterogeneous, good epidemiologic data are limited. In general, most authorities believe that clinically important paraneoplastic syndromes occur in less than 1% of cancer patients. The myasthenic syndromes are exceptions, in that 3% of patients with small-cell lung cancer (SCLC) develop Lambert-Eaton myasthenic syndrome (LEMS), and 16% of thymoma patients develop myasthenia gravis. Despite their rarity, paraneoplastic syndromes are important because they often indicate the presence of a potentially curable underlying cancer. The following case example of a patient with paraneoplastic cerebellar degeneration illustrates this point.

**APPROACH TO DIAGNOSIS**

**Case 2 Presentation**

A 52-year-old woman presents to a neurologist complaining of 3 months of slowly worsening gait instability. Her colleagues have mentioned that her speech sounds...
different. On examination, cognition is normal. The patient is dysarthric and has difficulty repeating the sequence “Pa-Ta-Ka.” Saccades are hypermetric bilaterally. Strength and sensation are normal, but rapid alternating movements are irregular bilaterally. Appendicular ataxia is mild but clearly present. Reflexes are normal. Gait is wide-based and moderately unsteady. Tandem gait is impossible.

- What is the differential diagnosis of a subacute pan-cerebellar syndrome?

**Differential Diagnosis**

Diagnoses to consider in this patient include infectious or postinfectious cerebellitis; demyelinating disease; prion diseases (eg, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease); stroke; hypothyroidism; primary degenerative diseases (eg, multiple system atrophy, progressive supranuclear palsy, cortico-basal degeneration, Huntington’s disease); hereditary illnesses (eg, adrenomyeloneuropathy, spinocerebellar ataxia); nutritional deficiencies (eg, vitamin E deficiency, vitamin B₁₂ deficiency with subacute combined degeneration); and alcoholic, hereditary, or paraneoplastic cerebellar degeneration (PCD). The pace of the illness (in this case, over 3 months) and a variety of historical features may be used to narrow this list considerably. Infectious and postinfectious diseases and stroke almost always present more acutely. Progressive cerebellar dysfunction as the sole manifestation of demyelinating disease, prion disease, or any of the degenerative, hereditary, or nutritional diseases mentioned above is extremely unusual. In the absence of associated symptoms, hypothyroidism is unlikely but should be ruled out with thyroid function tests. Alcoholism and hereditary illnesses can be addressed with additional history. PCD remains a possibility. Typically associated with SCLC, gynecologic cancers, or Hodgkin’s disease, PCD often presents months before the cancer is detected. Clinical symptoms and signs of midline and hemispheric cerebellar dysfunction evolve over weeks to a few months before stabilizing. Patients are often affected so severely that they have difficulty sitting without support and may need assistance with many activities of daily living. Bilateral, symmetric disease largely limited to the cerebellum and cerebellar pathways is typical.

**Case 2 Continued**

Further history reveals that the patient has not had any recent illnesses. She has never experienced transient neurologic dysfunction or possible optic neuritis. She denies weight gain, cold intolerance, fatigue, or constipation. She is a Mormon and has never consumed an alcoholic beverage. There is no family history of neurologic dysfunction. Additional examination reveals no evidence of myoclonus or any other movement disorder. Thyroid function tests and results on other routine laboratory tests are normal. Gadolinium-enhanced MRI of the brain is obtained, and no abnormality is detected.

- What investigations should be performed next?

**Diagnostic Tests to Detect a Primary Tumor**

At this point, PCD is the most likely diagnosis. Normal neuroimaging is the rule early in PCD; after months to a few years, diffuse cerebellar atrophy becomes apparent.
Appropriate diagnostic tests include CSF examination, paraneoplastic antibody screening, and screening for systemic cancer. In reported cases, CSF examination reveals a mild lymphocytic pleocytosis and mildly elevated protein and IgG levels. Oligoclonal bands are sometimes detected. The pleocytosis may resolve over time, so a normal CSF profile by no means rules out paraneoplastic disease.

Although antibodies are not always detected in unequivocal cases, antibody screening is an important component in the evaluation of a patient with paraneoplastic disease. Because many of these antibodies associate with multiple syndromes as well as cancers, a broad serologic panel should be obtained (Table 4). In rare circumstances, screening for paraneoplastic antibodies in the CSF may be helpful. Among patients with PCD, anti-Yo (also known as anti-Purkinje cell) antibodies are classically associated with ovarian cancer, and anti-Hu antibodies are usually observed in patients with SCLC. Overlap between syndromes is possible; for example, anti-Ri antibodies are found most frequently in the serum of breast cancer patients with opsoclonus-myoclonus syndrome but may also be present in cases of breast cancer and PCD. In fact, 9 different paraneoplastic antibodies have been associated with PCD. Occasionally, paraneoplastic antibody screening may facilitate detection of a second paraneoplastic syndrome in the same patient. For example, patients with PCD due to SCLC are sometimes found to have voltage-gated calcium channel antibodies and LEMS. Since LEMS may be very disabling but is treatable, early detection can be important. In patients with a clear paraneoplastic syndrome and no detectable antibodies, the diagnosis is based on exclusion of other causes.

Case 2 Continued

CSF examination reveals normal protein and IgG levels and 22 white blood cells/mm³, which are mostly lymphocytes. CSF cytology is negative for malignancy. A serum antibody panel identifies a high titer of anti-Yo antibodies. Pelvic ultrasonography followed by pelvic CT with contrast are unrevealing.

• What other options should be considered for identification of a primary tumor?

Imaging and Tumor Marker Testing

Given the association of PCD and anti-Yo antibodies with gynecologic and breast malignancies, most authorities would recommend further imaging (ie, mammography, CT of the chest and abdomen) and testing for appropriate serum tumor markers. In frequent cases when none of these tests identifies the primary cancer, positron emission tomography (PET) may be useful. A recent study found that PET was more than 80% sensitive for the identification of a primary tumor in this scenario; unfortunately, specificity was only 25%. At this time, PET is reserved for cases in which conventional techniques are inadequate to identify a primary tumor and a paraneoplastic syndrome is considered very likely. Because early detection of many cancers translates into higher cure rates, imaging techniques that promote early diagnosis are developing rapidly.

TREATMENT

Case 2 Continued

Mammography and contrast-enhanced CT scans of the chest and abdomen show no abnormalities. A full-body PET scan shows a tiny hypermetabolic area in the left ovary. Serum cancer antigen-125 level is 98 U/mL (upper limit of normal = 35 U/mL).

• How should this patient be treated?

As for most paraneoplastic syndromes, optimal treatment for PCD is unknown. Standard practice is to use a 2-pronged approach. First, one treats the underlying cancer, which in some cases has produced substantial improvement. Additionally, because of the presumed immunopathogenesis of these syndromes, immunosuppressant and immunomodulatory agents are used. Options include plasmapheresis or intravenous Ig to remove any humoral factor that may be responsible and suppressors of the T-cell response, such as corticosteroids, tacrolimus, or mycophenolate mofetil. Specific
protocols are generally reported on the basis of single cases or case series. LEMS and myasthenia gravis tend to improve significantly with treatment of the underlying tumor and immunosuppression with either plasmapheresis or intravenous Ig. Most other disorders respond poorly to any mode of treatment. For PCD, treatment of the underlying tumor often serves to prevent further disease progression, but improvement is uncommon.\textsuperscript{36}

Case 2 Conclusion

The patient undergoes laparotomy for staging, including total abdominal hysterectomy and bilateral salpingo-oophorectomy. A papillary serous carcinoma is found to be limited to the left ovary, and observation is recommended. Over the subsequent 10 years, the patient has no recurrence of her cancer. Trials of various immunosuppressants are administered without change in the level of neurologic disability. Because of ataxia, the patient remains wheelchair-bound and requires assistance for feeding, bathing, dressing, and toileting.

PITUITARY ADENOMA

EPIDEMIOLOGY AND PATHOGENESIS

Pituitary adenomas represent a common, heterogeneous group of benign tumors of the anterior pituitary gland. These tumors are generally classified by the cell of origin. For example, lactotrophs (prolactin-producing cells of the anterior pituitary) give rise to prolactinomas. Pituitary adenomas are often further classified as microadenomas (< 10 mm in diameter) or macroadenomas (≥ 10 mm in diameter). This distinction is easily made on MRI. Tumor size is relevant because macroadenomas may produce mass effect upon neighboring structures.

The estimated prevalence of pituitary adenomas based on a meta-analysis of postmortem and radiographic data is between 14% and 23%.\textsuperscript{37} According to the latest data from the Central Brain Tumor Registry of the United States, pituitary tumors (primarily adenomas) are the first or second most common CNS tumor in patients aged 15 to 34 years.\textsuperscript{3} Epidemiologic data suggest that pituitary adenomas represent 10% to 15% of intracranial neoplasms. There are no well-established risk factors for pituitary adenomas, although some cases occur in association with the multiple endocrine neoplasia (MEN) type 1 syndrome or other rare familial tumor syndromes. Patients with MEN type 1 develop tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells. The disorder is inherited in an autosomal dominant fashion.

Any of the hormones secreted by the normal pituitary gland may be synthesized and secreted by adenomas. These include prolactin, growth hormone (GH), thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH), β-lipotropin, luteinizing hormone, and follicle-stimulating hormone. The hormonal predilection of a given pituitary adenoma may be determined by tissue immunohistochemistry after the tumor is resected or by serum testing. These tumors may secrete 1 or several hormones, and approximately one third do not secrete any hormone at all. The latter are sometimes referred to as “null cell” or nonfunctional adenomas. Of

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cancer(s)</th>
<th>Paraneoplastic Syndrome(s)</th>
</tr>
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<tbody>
<tr>
<td>Anti-Hu</td>
<td>SCLC, neuroblastoma, prostate</td>
<td>Encephalomyelitis, sensory neuronopathy, cerebellar degeneration</td>
</tr>
<tr>
<td>Anti-Yo</td>
<td>Ovarian, breast, lung</td>
<td>Cerebellar degeneration</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>Breast, gynecologic, lung, bladder</td>
<td>Ataxia ± opsoclonus-myoclonus syndrome</td>
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<td>Anti-Tr</td>
<td>Hodgkin’s lymphoma</td>
<td>Cerebellar degeneration</td>
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<td>SCLC</td>
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<td>Stiff-person syndrome, encephalomyelitis</td>
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<td>Anti-Ma1</td>
<td>Lung, other</td>
<td>Brainstem encephalitis, cerebellar degeneration</td>
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<tr>
<td>Anti-Ma2</td>
<td>Testicular</td>
<td>Limbic and brainstem encephalitis</td>
</tr>
<tr>
<td>Anti-VGKC</td>
<td>Thymoma, SCLC</td>
<td>Neuromyotonia</td>
</tr>
<tr>
<td>Anti-MAG</td>
<td>Waldenström’s macroglobulinemia</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Anti-nAChR</td>
<td>Thymoma</td>
<td>Myasthenia gravis</td>
</tr>
</tbody>
</table>

MAG = myelin-associated glycoprotein; nAChR = nicotinic acetylcholine receptor; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel. (Adapted with permission from Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1548. Copyright © 2003 Massachusetts Medical Society. All rights reserved.)
the hormone-secreting adenomas, prolactin-secreting adenomas are much more common than other types. Prolactinomas are unique in that most are successfully treated with medical therapy alone.

**CLINICAL FEATURES**

**Case 3 Presentation**

A 19-year-old woman presents to her primary care physician with expressible galactorrhea, which she first noticed 3 months ago. She has never been pregnant. The patient experienced menarche at 13 years of age, followed by 1 year of irregular menses. Since that time, she has been amenorrheic. She complains of occasional headaches but no other neurologic symptoms. She denies having any visual abnormalities.

- **What are the typical presenting symptoms of pituitary adenomas?**

  Pituitary microadenomas frequently come to attention as a result of endocrine abnormalities due to hormone hypersecretion, as in this patient. Asymptomatic lesions are also common. In fact, incidental pituitary adenomas may be discovered on routine brain imaging in more than 20% of individuals. Macroadenomas cause symptoms via mass effect on visual structures, hormone hypersecretion, or a combination of both. Symptoms and signs of pituitary hypofunction are often observed in macroadenoma patients as well.

**Symptoms and Signs of Mass Effect**

Mass effect from a pituitary adenoma is the most common cause of optic chiasm dysfunction in adults, classically producing a bitemporal hemianopsia. Bitemporal scotomas, markedly asymmetric visual loss, foggy or dim vision, and superior bitemporal hemianopsia are often seen as well. These effects are explained by tumor expansion and compression of the optic chiasm, which lies anterior and superior to the pituitary gland. Oculomotor paralysis sometimes occurs when a incidental adenoma extends laterally to invade the cavernous sinus. Cavernous sinus contents include cranial nerves III, IV, and VI; the first 2 divisions of cranial nerve V; and sympathetic nerves en route to the eye. A pituitary lesion may compromise any of these structures. Rarely, compression of the internal carotid artery in the cavernous sinus may occur and produce cerebral ischemia. As with any space-occupying brain lesion, symptoms of increased intracranial pressure may be elicited. Headaches affect 50% of patients with macroadenoma. Although migraine headache is most common, cluster headache and related headache subtypes are known to occur. Uncommonly, pituitary adenomas may invade the hypothalamus and produce autonomous dysregulation, hypothermia, diabetes insipidus, or somnolence. Several other rare presentations have been described, which include third ventricle compression with obstructive hydrocephalus, CSF rhinorrhea, and seizures from temporal lobe indentation.

**Endocrine Manifestations**

Clinical manifestations due to hormone excess depend on the pituitary hormone involved. The endocrine manifestations of pituitary adenomas may result from an interruption of communication between the hypothalamus and the pituitary gland or from direct hormone secretion by the tumor itself. In fact, mass effect from any lesion on the pituitary infundibulum may produce hyperprolactinemia. This phenomenon is termed the “stalk effect” and tends to cause mildly elevated prolactin levels (usually 100–200 ng/mL). Marked hyperprolactinemia (> 200 ng/mL) is generally seen with true prolactin-secreting tumors. The stalk effect occurs because prolactin secretion is under inhibitory control by various hypothalamic factors, of which dopamine is the most important. As dopamine is released from the hypothalamus, it descends through the portal vessels to the anterior pituitary gland, where it inhibits the release of prolactin by prolactin-secreting cells (lactotrophs). Mass effect on the pituitary stalk can impair dopamine transfer to the anterior pituitary and thereby produce lactotrophi hyperfunction.

**Prolactin-secreting tumors.** Subtle changes in prolactin levels can alter menses. As a result, prolactinomas often present in female patients of childbearing age as amenorrhea, oligomenorrhea, or infertility. Galactorrhea occurs commonly and may be the only detectable abnormality on physical examination. Slight changes in prolactin levels are less evident in male patients; thus, prolactin-secreting macroadenomas may exert hormone effects that go unnoticed for months or years. Such tumors may not come to clinical attention until a male patient develops headache and visual changes due to optic chiasm compression. Typical symptoms of prolactin excess in men, often recognized only in retrospect, include impotence, gynecomastia, galactorrhea, and loss of libido. When a prolactinoma becomes large enough to compress normal pituitary tissue, thyroid and adrenal function are often impaired as well.

**GH-secreting tumors.** The clinical manifestations of adenomas that secrete GH are quite different from those seen with prolactinomas. GH hypersecretion in adults produces acromegaly, a syndrome characterized by acral growth and progonathism, often in combination with visceromegaly, headache, and diabetes. Acromegalic patients have a highly characteristic facial
appearance. Diagnosis is frequently delayed because of the rarity of the disorder and the development of characteristic features over months to years.

**ACTH-secreting tumors.** Adenomas that produce ACTH may cause a syndrome of cortisol excess known as Cushing disease. Cushing disease refers specifically to hypercortisolism that results from pituitary hypersecretion of ACTH. In contrast, Cushing syndrome is a state of cortisol excess due to exogenous steroids or primary hyperadrenalinism. Regardless of the cause, hypercortisolism is characterized by hirsutism, abdominal striae, hypertension, hypokalemia, acne, menstrual irregularity, centripetal obesity, immunosuppression, myopathy, and psychosis.

**Pituitary Apoplexy**

Pituitary apoplexy is an uncommon syndrome characterized by the sudden onset of severe headache, visual loss, ophthalmoplegia, and change in level of consciousness, often with CSF abnormalities (ie, hemorrhage or pleocytosis and elevated protein). This life-threatening condition occurs when a pituitary tumor outgrows its blood supply; the result is hemorrhagic infarction with mass effect on the suprasellar space and cavernous sinuses. Pituitary apoplexy is the presenting feature of a pituitary tumor in less than 2% of cases.\(^4^1\) Predisposing factors include Sheehan syndrome from postpartum hemorrhage, trauma, angiography, diabetic ketoacidosis, bromocriptine, RT, and cardiac surgery. The management of pituitary apoplexy includes urgent steroids and transsphenoidal surgery. Although recovery is expected in patients who receive prompt treatment, panhypopituitarism is common after pituitary apoplexy.

**APPROACH TO DIAGNOSIS**

**Case 3 Continued**

The neurologic and general examinations are normal. Visual field testing is normal. Endocrinologic laboratory screening reveals an elevated prolactin level of 412 ng/mL. MRI shows a subtle prominence of the left pituitary lobe that is hypointense on T1 sequences and hyperintense on T2 sequences. Unlike the normal pituitary tissue, the lesion does not enhance with gadolinium.

- **What diagnosis is suggested by these MRI findings?**

**Diagnostic Findings on Neuroimaging**

The MRI appearance described for this patient is typical of a microprolactinoma. In most cases, these lesions are hypointense on T1, hyperintense on T2, and non–contrast-enhancing (Figure 4). Most are located laterally within the gland. Dynamic contrast-enhanced, dedicated pituitary imaging may substantially increase the sensitivity for tumor detection to approximately 90%.\(^4^2\) Although identification of a focal mass is suggestive of an adenoma, pituitary stalk deviation may be observed in normal pituitary glands and should not be taken as strong evidence of tumor. In patients who have a contraindication to MRI, dedicated pituitary CT nearly achieves the sensitivity of MRI for adenoma detection and may better evaluate adjacent bony abnormalities.

Unlike microadenomas, which are sometimes challenging to visualize, macroadenomas are easily identified; however, they are more likely to be confused with other sellar region masses. Macroadenomas often have cystic, necrotic, or hemorrhagic areas that lead to a heterogeneous appearance on T2 images. In other cases, they have the same signal characteristics as gray matter. As for microadenomas, gadolinium enhancement is unusual, and most lesions show less enhancement than normal pituitary tissue. The primary role of MRI in patients with macroadenomas is determination of which
adjacent structures are involved with tumor.\textsuperscript{42} This information is critical for surgery and RT planning.

- **What is the differential diagnosis of a pituitary mass?**

**Differential Diagnosis of a Pituitary Mass**

Although the large majority of mass lesions confined to the pituitary on MRI represent adenomas, a variety of other diagnoses must be considered (Table 5). Pituitary carcinomas are extremely unusual, aggressive lesions that are capable of systemic metastasis and cannot be readily distinguished from adenomas on imaging or even histology.

Important differential diagnoses also include other benign tumors, such as craniopharyngioma and meningioma. Because these neoplasms do not often involve the pituitary fossa and because they generally arise from suprasellar structures, MRI diagnosis is usually straightforward. Craniopharyngiomas may also be distinguished from pituitary lesions because they are frequently calcified and cystic. Meningiomas are dural-based, homogeneously enhancing lesions that often produce bony changes. Rathke cleft cysts, dermoid and epidermoid cysts, and vascular anomalies have different signal characteristics on MRI than pituitary adenomas.

Pituitary metastases may be diagnostically challenging from the standpoint of imaging. The presence of diabetes insipidus is a typical presenting symptom that may help to distinguish pituitary metastasis from a benign adenoma.

One of the most challenging differential diagnoses is lymphocytic hypophysitis, an inflammatory syndrome that produces headache, visual field abnormalities, and hypopituitarism. Lymphocytic hypophysitis is strongly associated with pregnancy and the postpartum period and is 6 times more likely to occur in women than men.\textsuperscript{43} Enhancement of the pituitary stalk and inferior hypophalamsus may be helpful in distinguishing this lesion from an adenoma.

Other systemic inflammatory or granulomatous diseases may involve the pituitary and masquerade as adenomas. Examples include sarcoidosis, Wegener’s granulomatosis, Langerhans’ cell histiocytosis, and mycobacterial or spirochetal infections.

Finally, non-neoplastic pituitary hyperplasia may be mistaken for a pituitary adenoma. Examples of physiologic pituitary hyperplasia include lactotroph hyperplasia (which may be observed during pregnancy) and thyrotroph hyperplasia (which occurs in patients with long-standing primary hypothyroidism).

- **What additional tests are needed to confirm the diagnosis?**

### Table 5. Differential Diagnosis of a Sellar Mass

<table>
<thead>
<tr>
<th>Benign tumors</th>
<th>Inflammatory diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma</td>
<td>Langerhans’ cell histiocytosis</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Lymphocytic hypophysitis</td>
</tr>
<tr>
<td>Cysts</td>
<td>Malignant tumors</td>
</tr>
<tr>
<td>Arachnoid</td>
<td>Chordoma</td>
</tr>
<tr>
<td>Dermoid</td>
<td>Germ cell tumor</td>
</tr>
<tr>
<td>Epidermoid</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Rathke’s cleft</td>
<td>Pituitary carcinoma</td>
</tr>
<tr>
<td>Infections</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Cysticercosis</td>
<td>Metastatic tumors</td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>Pituitary hyperplasia</td>
</tr>
<tr>
<td>Pituitary abscess</td>
<td>Vascular anomalies</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Carotid artery aneurysm</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Cavernous-carotid fistula</td>
</tr>
</tbody>
</table>


### Approach to the Patient with Suspected Pituitary Adenoma

Because the case patient has clinical, radiologic, and laboratory evidence consistent with microprolactinoma, no additional investigation is required to confirm the diagnosis in this case. For patients in whom a pituitary adenoma is suspected but not yet confirmed, a neurologic examination with careful attention to visual fields is the first step in the evaluation. Because progressive visual field loss often necessitates surgical management, referral to an ophthalmologist or neuro-ophtalmologist for formal visual field assessment is warranted in most cases. Even patients with microadenomas can have visual field abnormalities due to previous compression or, in some cases, vascular shunting.\textsuperscript{39} Visual field testing should be repeated within a few days after surgery if the patient is able to comply. Serial neuro-ophtalmologic and neuroimaging examinations may be performed at 6 months and 12 months postoperatively, and yearly after that if the patient is stable. Serum hormone testing is also required for accurate diagnosis. Provocative and dynamic testing of hormone levels may be necessary to adequately define syndromes of hormone excess or deficiency. This evaluation should generally be conducted in conjunction with an endocrinologist, but a summary of frequently used tests is presented in Table 6.\textsuperscript{39,44} Although hormone deficiencies are not often helpful diagnostically, appropriate replacement must be instituted. As previously noted,
Table 6. Limited Endocrine Evaluation in Patients with Suspected Pituitary Adenoma

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Diagnostic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>Prolactin levels &gt; 200 ng/mL reliably indicate the presence of a prolactinoma; elevated levels that are &lt; 200 ng/mL may be the result of a microadenoma, medication effect, or any other sellar mass.</td>
</tr>
<tr>
<td>GH</td>
<td>Acromegaly is diagnosed in the appropriate clinical context when basal GH levels are elevated on 2 occasions. Because GH stimulates hepatic IGF-1 secretion, serum IGF-1 elevation is expected. For borderline cases, GH measurement after suppression by an oral glucose load is useful.</td>
</tr>
<tr>
<td>ACTH</td>
<td>Elevated 24-hr urine free cortisol excretion associated with at least high-normal serum ACTH concentration suggests the presence of an ACTH-secreting adenoma. More sophisticated testing may be necessary to draw definitive conclusions.</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1.

dedicated pituitary neuroimaging is the third critical component in the evaluation of patients with suspected pituitary adenoma.

The question of how to approach the patient with an incidentally discovered pituitary mass is unresolved. Most practitioners monitor these asymptomatic patients with serial visual acuity and visual field testing and gadolinium-enhanced MRI. Although most incidentally discovered adenomas do not secrete hormones, some physicians check hormone levels periodically as well. Intervention is recommended for patients who experience tumor growth, visual loss, displacement of the optic chiasm by imaging, or hypopituitarism.

MANAGEMENT

Case 3 Continued

Medical therapy with cabergoline is initiated. Galactorrhea subsides within 2 weeks. Serial MRI scans show near complete resolution of the lesion. Prolactin levels decrease to slightly above normal values.

• What treatment options are available for patients with a pituitary adenoma?

Goals of therapy for pituitary adenomas include reversing the endocrine manifestations of excess hormone secretion, restoring pituitary function, preserving healthy pituitary tissue, and preventing damage to critical structures in close proximity to the pituitary gland. Because pituitary adenoma is a heterogeneous disease, each patient must be treated with an individualized approach.

Treatment of Asymptomatic Tumors

Asymptomatic microadenomas do not require treatment, as longitudinal experience proves that progression is uncommon. Patients with microprolactinomas whose only symptom is amenorrhea may opt for estrogen replacement therapy instead of dopamine agonists. Despite concerns that estrogen may promote adenoma growth, ample data demonstrate that exogenous estrogen has no effect on tumor progression.

Surgery

With the exception of prolactinomas, resection of symptomatic pituitary adenomas is the first-line treatment. Surgery is nearly always necessary in patients with macroadenomas that are causing progressive visual field loss. Pituitary apoplexy is always an indication for urgent surgery. The transsphenoidal approach allows for direct visualization of the pituitary gland and tumor and is well-tolerated. Infrequent complications include CSF leak and hypopituitarism. Most (nonprolactinoma) microadenomas are curable with surgery alone, whereas 50% or fewer macroadenomas may be cured with surgery alone. In rare patients with prolactinoma who are refractory to medical therapy or cannot tolerate it, surgical resection may be performed, although efficacy in this setting is limited.

Medical Therapy

Prolactinomas of any size are primarily treated medically, most often with ergot-derived dopamine agonists, such as bromocriptine, pergolide, and cabergoline. Bromocriptine and pergolide are both D1 and D2 receptor agonists, whereas cabergoline acts at the D2 receptor alone. All of these agents inhibit the synthesis and secretion of prolactin. Multiple studies have shown that dopamine agonists are effective in shrinking pituitary adenomas and in lowering serum prolactin levels in most patients, but no studies have identified the superior agent. An attractive feature of cabergoline is its 80-hour half-life, which allows for once- or twice-weekly administration and improved patient compliance. This is in contrast to bromocriptine, which is administered 2 or 3 times daily. Side effects of cabergoline are reported to be less troublesome than those observed in bromocriptine-treated patients. Also of note is that cabergoline may be effective in patients who have failed treatment with bromocriptine. The duration of dopamine agonist therapy in patients with prolactinoma is unclear, and many physicians treat indefinitely. Recent data indicate that cabergoline may be safely withdrawn in patients whose tumor becomes undetectable on MRI and whose serum prolactin level normalizes, although
long-term follow-up of these patients has not yet been reported. Any of the dopamine agonists may cause nausea, orthostatic hypotension, fatigue, and depression. These side effects tend to improve with time and can be prevented by slow dose titration. A rare but serious side effect of medical therapy occurs when tumor shrinkage reveals a dural or sellar defect. The result is CSF rhinorrhea, and surgical management is indicated. Very recent data indicate that cabergoline therapy is associated with cardiac valve regurgitation. The significance of these findings remains to be determined.

Medical therapies other than dopamine agonists are used in the management of acromegaly when a surgical cure cannot be achieved. Octreotide, for example, is a somatostatin analog that normalizes GH levels and can decrease tumor size. Potential side effects include diarrhea, nausea, and cholelithiasis. Pegvisomant, a novel GH-receptor antagonist, is a second-line medical therapy for refractory acromegaly. Although the agent is highly effective in reversing effects of high hormone levels, it has no impact on the tumor mass. Pegvisomant is costly, requires daily subcutaneous injections, and may produce abnormalities on liver function testing.

Radiotherapy

Because of modest efficacy, high rates of hypopituitarism, and a small risk of optic neuropathy, RT is not employed as a primary treatment modality in patients with pituitary adenomas. It is reserved for residual tumor after surgery or for tumor recurrence. Anti-tumor effects may not be seen for months to years after radiation administration.

Case 3 Conclusion

After 2 years of cabergoline therapy, the patient remains asymptomatic and MRI shows no definite residual abnormality. The patient complains of daytime fatigue that may be related to cabergoline, but she and her physician are reluctant to change the treatment regimen. Her physician plans to continue treatment indefinitely.

CONCLUSION

PCNSL is an increasingly common primary brain tumor that develops most frequently in older adults and in HIV-infected patients. Important treatment modalities include methotrexate-based chemotherapy and WBRT. In patients with favorable prognostic factors, survival longer than 5 years is possible. At present, patients who are treated with WBRT are at high risk for developing progressive neurotoxicity that is fatal within months to years. Effective chemotherapy regimens that eliminate the need for WBRT are now being developed. Because limited extranodal lymphoma that occurs outside the nervous system is often curable, one hopes that similar success will be achieved for PCNSL in the near future.

Paraneoplastic syndromes are a heterogeneous group of disorders that sometimes improve with early treatment of the underlying cancer, once diagnosed, or with immunosuppressive therapies. Multimodal treatment is expected to play an increasingly important role in the management of these disorders in the future.

Pituitary adenoma is a common and heterogeneous entity that is frequently discovered incidentally. When these benign tumors cause symptoms due to mass effect or dysregulated hormone secretion, a variety of effective treatments are available. Dopamine agonist therapy effectively cures most prolactinomas, whereas surgery is the mainstay of treatment for other pituitary adenoma subtypes. Because treatment options are constantly evolving, multidisciplinary teams comprised of neurologists, endocrinologists, neurosurgeons, and ophthalmologists are necessary to provide optimal care.

REFERENCES