CLINICAL PROBLEM-SOLVING

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Stalking the Diagnosis

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

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A 22-year-old man presented with progressive neurologic decline. A year before presentation, painless vision loss had occurred in the left eye, followed by the right eye. During the next 4 to 6 months, diffuse numbness, limb stiffness, whole-body weakness, and urinary incontinence had developed. Additional symptoms included a weight loss of 6.8 kg during the previous year, disorientation, and progressive inability to care for himself.

The patient was from Pakistan and had moved to central California 3 months before symptom onset. He had worked as a delivery driver. He did not smoke tobacco, drink alcohol, or use any recreational drugs. His family history was unremarkable.

The patient had received a clinical diagnosis of multiple sclerosis from a neurologist on the basis of symptoms and findings on imaging that were suggestive of demyelination. At that time, he started treatment with natalizumab but had no response. Subsequently, treatment was transitioned to interferon beta-1a. His symptoms continued to progress, and his family brought him to the emergency department of an academic medical center at the recommendation of his local physician.

This previously healthy young man has a history of additive, progressive ocular and neurologic symptoms that were attributed to multiple sclerosis but did not abate with therapy for this condition. Diseases that cause acute, isolated, painless monocular blindness typically localize to either the posterior pole of the eye or the optic nerve. The second phase of the illness suggested new involvement of upper motor neurons, sensory pathways, and autonomic tracts that control sphincter function. Possibilities for neuroanatomical localization include the cervicothoracic spinal cord, the brainstem, the frontal and parietal lobes, and their associated deep white-matter tracts. The patient's history of residing in Pakistan and central California poses a risk of endemic infectious disease, such as coccidioidomycosis, tuberculosis, or reactivation of measles leading to subacute sclerosing panencephalitis.

On examination, the patient's temperature was 36.9°C, the blood pressure 102/55 mm Hg, the pulse 75 beats per minute, and the oxygen saturation 98% while he was breathing ambient air. He appeared chronically ill. The results of cardiovascular, pulmonary, and abdominal examinations were normal. On neurologic examination, he was awake and oriented to being in a hospital but not to the city or date. He followed simple commands and had a paucity of speech. The pupils were equal but nonreactive to light. On confrontation testing, visual acuity was severely impaired bilaterally, with perception of light and finger movements only. The arms and legs had de-

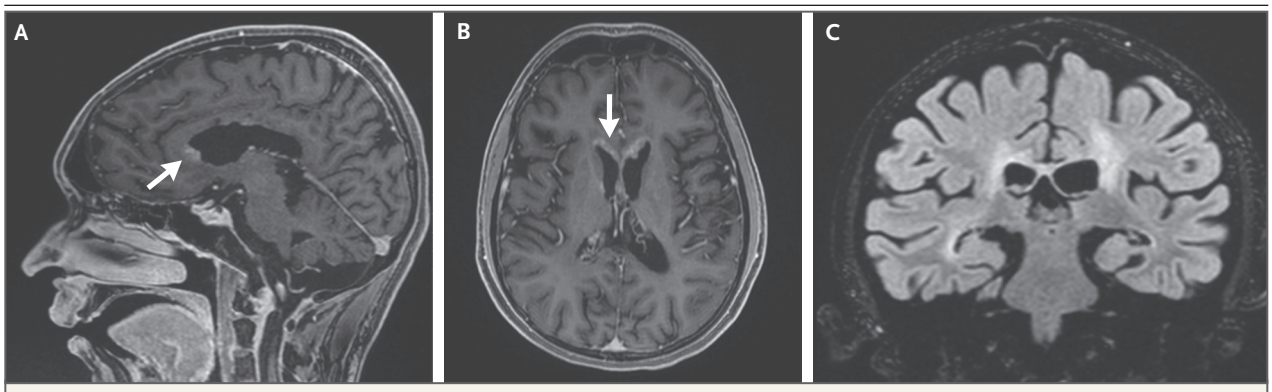

Figure 1. MRI of the Head.
Sagittal and axial images (Panels A and B, respectively) show nodular ependymal lesions (arrows) and leptomeningeal enhancement. A coronal image (Panel C) shows changes in the periventricular white matter.

creased muscle bulk and increased tone and paratonia. Reflexes were 3+ throughout, and the Babinski sign was present bilaterally. Sensation to light touch was intact. Results of cerebellar testing were normal. The patient was unable to ambulate without assistance.

The patient has profound vision loss; the nonreactive pupils indicate localization anterior to the optic chiasm. The most striking findings on neurologic examination are the cognitive deficits, spastic quadriparesis, and vision deficits, which together suggest a multifocal disease process. Because the initial history suggested the possibility of spinal cord disease, it is important to check the sensory level.

The course of this patient's illness would be unusually protracted for many central nervous system (CNS) infections. In addition, aggressive cancers that can occur in his age group would be likely to result in additional nonneurologic manifestations or even in death if they would be untreated for this length of time.

The complete blood count and blood chemical profile were normal, with the exception of a sodium level of 148 mmol per liter. A lumbar puncture was performed, and analysis of the third tube of cerebrospinal fluid (CSF) aspirate revealed clear fluid with a white-cell count of 11 per cubic millimeter (reference range, <6), of which 94% were lymphocytes and 6% were monocytes, as well as a red-cell count of 5 per cubic millimeter, a glucose level of 44 mg per deciliter (2.4 mmol per liter), and a protein level of 110 mg per deciliter (reference range, 15 to 50). Oligoclonal bands were present.

Magnetic resonance imaging (MRI) of the head revealed areas of nodular ependymal and leptomeningeal enhancement on a background of extensive signal abnormality in the periventricular white matter (Fig. 1). In addition, there was symmetric signal abnormality along the optic tracts. Findings on MRI of the spinal cord, performed with and without the administration of contrast material, were normal.

The CSF analysis provides evidence of inflammation in the CNS, which essentially limits the diagnostic considerations to three categories of CNS disease: neoplastic, infectious, and noninfectious inflammatory processes. Although oligoclonal bands are most commonly associated with multiple sclerosis, they are a nonspecific finding that can be seen with other disease processes. Likewise, although hypoglycorrhachia often occurs with acute or chronic infectious meningitis, it can be a feature of any of these three categories of CNS disease.

The neuroimaging findings indicate intracranial involvement (i.e., involvement of the optic tracts, meninges, and white matter) without apparent spinal cord disease, although this possibility cannot be ruled out definitively. Hyperintensity in the periventricular white matter is an abnormal but nonspecific finding. Subependymal enhancement is a rare, striking finding that substantially narrows the range of diagnostic considerations. When such enhancement is described as nodular, a neoplastic cause such as

glioma, primary CNS lymphoma, ependymoma, a germ-cell tumor, or leptomeningeal metastasis is the most likely explanation, although a granulomatous process such as sarcoidosis or granulomatous angiitis of the CNS is also possible. Most infectious causes of chronic subependymal enhancement and ventriculitis, including tuberculosis, syphilis, and cryptococcosis, are associated with a thinner, more linear pattern of enhancement.

Given the presence of contiguous intracranial meningeal enhancement and the abnormal CSF findings, a chronic form of meningitis and ventriculitis, such as CNS coccidioidomycosis or tuberculosis, should be considered. This possibility is unlikely, however, because of the substantial neurologic deficits without evident cerebral infarction or hydrocephalus, the protracted disease course, and the absence of headache.

Blood and CSF cultures for bacteria and stains and cultures for mycobacteria and fungi were negative, as were a polymerase-chain-reaction (PCR) assay of the CSF for *Mycobacterium tuberculosis*, CSF and serum tests for cryptococcal antigen, and tests for herpes simplex virus, varicella–zoster virus, West Nile virus, dengue, chikungunya, JC virus, and human herpesvirus 6. Upper and lower endoscopy was unrevealing. Examination of endoscopic biopsy specimens revealed no evidence of *Tropheryma whipplei*.

Tests for antinuclear, anti–double-stranded DNA, anti-Ro (SSA), anti-La (SSB), tissue transglutaminase, and antineutrophil cytoplasmic antibodies were negative, as was a test for antibodies to aquaporin-4. Cytologic and flow cytometric studies of the CSF were unrevealing.

Biopsy specimens of the dura, cortex, and periventricular white matter showed increased cellularity, composed predominantly of macrophages and scattered lymphocytes.

Although most CSF PCR assays for viral pathogens have a reasonably high sensitivity for the detection of CNS infection, the CSF PCR assay for *M. tuberculosis* has variable sensitivity. Reactivation of latent tuberculosis has been associated with natalizumab therapy, but the protracted clinical course makes this diagnosis unlikely. In rare cases, Whipple's disease can cause chronic CNS infection, but the negative endoscopic studies make this diagnosis unlikely, since most patients have concomitant gastrointestinal involvement. The absence of antibodies to aquaporin-4 argues against a diagnosis of neuromyelitis optica, but this test was probably not necessary in light of the normal findings on MRI of the spinal cord.

The findings on brain biopsy are nonspecific. The absence of diagnostic findings could be explained by a sampling error. If representative tissue was obtained, the biopsy results would rule out many types of cancer and granulomatous disease, under the assumption that there is no underlying immunocompromise preventing granulomas from forming.

On hospital day 10, the sodium level abruptly increased to 165 mmol per liter. The daily urine output was approximately 3 to 4 liters and the urine osmolality 132 mmol per kilogram (reference range, 300 to 900). The patient received free water replacement through his feeding tube. The prolactin level was 48 μg per liter (reference range, 3.6 to 18.0), the corticotropin level 7 ng per liter (reference range, 6 to 50), the follicle-stimulating hormone level 0.2 IU per liter (reference range, 1 to 12), and the luteinizing hormone level 0.1 IU per liter (reference range, 0.6 to 12.1). The cortisol level was 3 μg per deciliter (reference range, 4 to 19) and increased to 12 μg per deciliter after the administration of synthetic corticotropin. The thyrotropin level was 0.24 mIU per liter (reference range, 0.45 to 4.12) and the free thyroxine level 8 pmol per liter (reference range, 10 to 18). The patient started treatment with hydrocortisone, followed by levothyroxine.

The constellation of hyperosmolality, polyuria, and inappropriately dilute urine is characteristic of diabetes insipidus. This condition is likely to be of central origin, given the close proximity of CNS disease to the pituitary gland and the additional evidence of panhypopituitarism. The mild hypernatremia that occurred earlier in the disease course probably indicated early, partially compensated diabetes insipidus.

Dedicated imaging of the pituitary gland should be performed, since lesions in and around the sella turcica may be missed on routine MRI of the head. The differential diagnosis of panhypopituitarism that is not caused by hypophysectomy includes cancer (primary pituitary tumors, extranodal natural killer–T-cell lymphoma, and metastases), autoimmune disease (lymphocytic hypophysitis), granulomatous processes (sarcoido-

sis and lymphomatoid granulomatosis), infiltrative diseases (histiocytosis and amyloidosis), and rare cases of infection (tuberculosis, pituitary abscess, and syphilis).

MRI of the pituitary gland, performed with and without the administration of contrast material, revealed the absence of normal high signal intensity in the posterior lobe, a finding consistent with diabetes insipidus, as well as diffuse infundibular thickening (Fig. 2). The patient was scheduled to undergo transsphenoidal biopsy of the pituitary lesion.

Craniopharyngioma is a suprasellar tumor that occurs in young people and can have cystic components. However, this tumor would not explain the progressive, systemic findings in this case. The pituitary and infundibular findings point to a limited group of potential diagnoses.

Both neurosarcoidosis and various histiocytoses can cause indolent, progressive CNS disease, either in isolation or as part of a broader systemic illness. These conditions share an inflammatory CSF profile and can result in lesions of the meninges, sella turcica, and ventricular system. In this young man, the early blindness with presumed involvement of the optic nerves and the extensive white-matter disease point to sarcoidosis as the most likely diagnosis. The determination of whether he is the rare person with sarcoidosis who has disease limited to the CNS or whether he has neurosarcoidosis with subclinical disease in other organs awaits assessment of other extraneurologic sites.

Transsphenoidal biopsy of the pituitary lesion was performed, and examination of the biopsy specimen revealed histologic findings consistent with a suprasellar CNS germinoma (Fig. 3). The CSF human chorionic gonadotropin level was elevated at 4.5 IU per liter (reference range, <1.1). The patient ultimately received a diagnosis of a pituitary CNS germinoma with presumed complication by neoplastic meningitis and parenchymal infiltrative disease leading to profound neurologic disability, although definite tissue-based or cytologic evidence of disease in these compartments was lacking. The patient started chemotherapy with etoposide and carboplatin, followed by radiation therapy. Ten months after diagnosis, he had a clinical and radiologic response to treatment but continued to have hypopituitarism, for which he received hydrocortisone and levothyroxine, as well as substantial neurologic disability, for which he received assistance with all activities of daily living.

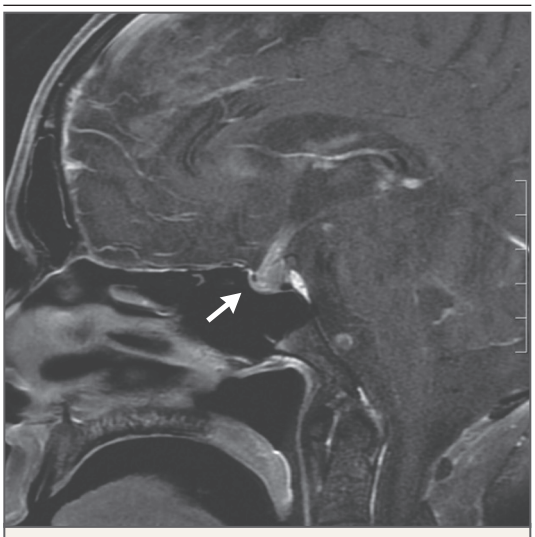

Figure 2. MRI of the Pituitary Gland.
A T1-weighted, fat-suppressed image, obtained after the administration of contrast material, shows abnormal diffuse infundibular thickening (arrow) and the absence of normal high signal intensity in the posterior lobe.

COMMENTARY

This patient's disease course of early ocular manifestations (thought to be due to optic neuritis), later followed by neurologic deficits involving upper motor neurons, appropriately prompted consideration of multiple sclerosis. Although multiple sclerosis is the CNS disease that most frequently causes permanent disability in young adults, establishing the diagnosis can be challenging. Diagnostic criteria require identification of a compatible demyelinating syndrome (e.g., optic neuritis, a brainstem or cerebellar syndrome, or transverse myelitis) with objective neurologic findings disseminated in both space and time (i.e., damage to different parts of the CNS occurring on different dates).[1] Misdiagnosis of multiple sclerosis is common; 30 to 67% of patients who are referred to multiple sclerosis centers ultimately receive a different diagnosis.[1] In one case series, the most common alternative diagnoses included migraines, functional disorders, and neuromyelitis optica spectrum disorder; other inflammatory conditions can also mimic the disease.[2]

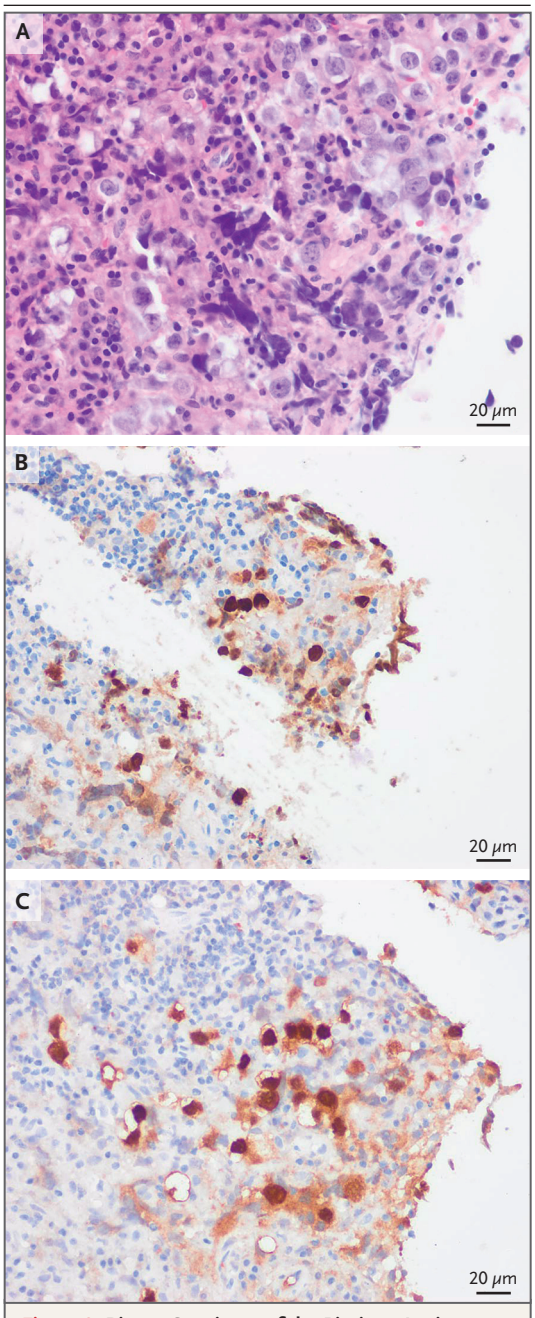

Figure 3. Biopsy Specimen of the Pituitary Lesion.

Routine hematoxylin and eosin staining shows a background of dense inflammation and scattered large epithelioid tumor cells with centrally placed round-to-oval nuclei, prominent nucleoli, and a moderate amount of pale-to-clear cytoplasm (Panel A). On immunohistochemical staining, the tumor cells are positive for the germ-cell markers SALL4 and OCT4 (Panels B and C, respectively). The findings are diagnostic of germinoma.

The detection of nodular ependymal and meningeal enhancement and CSF pleocytosis expanded the differential diagnosis to include a range of infectious, infiltrative, and neuroinflammatory disorders. Many conditions can involve the meninges, including bacterial, mycobacterial, fungal, viral, autoimmune, and malignant processes. Chronic meningitis, which is defined as meningitis with symptoms lasting longer than 4 weeks and with CSF pleocytosis, is most commonly caused by atypical bacteria, fungi, or a noninfectious process.[3] Imaging studies can help to delineate the pattern of meningeal enhancement (e.g., leptomeningeal, pachymeningeal, or basal meningeal) and thereby focus the differential diagnosis. For example, bacterial and viral meningitides tend to produce a thin, linear pattern of leptomeningeal enhancement, whereas fungal and neoplastic meningitides are often associated with a thicker, nodular pattern of enhancement.[4]

Neoplastic meningitis is an uncommon cause of CSF pleocytosis that can result from hematologic cancers, metastatic solid tumors, or in rare cases, primary brain cancers. Metastasis to the CSF can be due to either hematogenous spread or contiguous extension from brain parenchymal tumors or bony disease.[5] The standard method for diagnosing neoplastic meningitis is the detection of abnormal cells on CSF cytologic studies or of a monoclonal population on flow cytometric studies. Cytologic examination of a single CSF specimen has low sensitivity (70% in one series), but the sensitivity increases to approximately 90% when specimens from three serial lumbar punctures are assessed.[5] The presence of ependymal, leptomeningeal, or dural enhancement on MRI is consistent with neoplastic meningitis.[4]

The development of diabetes insipidus provided an important diagnostic breakthrough in this difficult case, leading the discussant to consider diseases in the pituitary gland and hypothalamus. Possibilities include benign tumors (e.g., pituitary adenomas), cancers (both primary CNS cancers and metastases), inflammatory disorders (e.g., neurosarcoidosis, Langerhans-cell histiocytosis, and granulomatosis with polyangiitis), infections, and congenital abnormalities.[6] Symptoms associated with sellar lesions vary, depending on the size of the lesion, whether the lesion secretes hormones, and whether growth of the lesion interferes with hypothalamic or pituitary function. Among patients with nonsecretory lesions, the most common presentations

include vision impairment, hypopituitarism, hyperprolactinemia due to compression of the pituitary stalk (infundibulum), and headache. Diabetes insipidus and cranial neuropathies are rare complications.[7]

CNS germ-cell tumors are rare primary brain tumors that occur most often in children and young men. These tumors have a propensity to occur in midline structures, including the neurohypophysis and pineal gland, where they can lead to headache, hydrocephalus, ocular symptoms, and pituitary dysfunction.[8] CNS germ-cell tumors can also spread throughout the CNS, including the brain parenchyma (where they can mimic demyelinating disease on imaging), the optic tracts, and the CSF, as was seen in this case.[9-11] As such, when these tumors are identified, imaging of the whole neuraxis and testing of the CSF should be performed.

Given the rarity and nonspecific presentation of CNS germ-cell tumors, the diagnosis can be challenging and is often delayed. Across many case reports, patients with CNS germ-cell tumors initially received such disparate diagnoses as multiple sclerosis (with oligoclonal bands having been noted in some cases), chronic infectious meningitis, and lymphocytic hypophysitis.[9-12] Although definitive diagnosis requires histologic confirmation, several findings can suggest the presence of an underlying CNS germ-cell tumor. Characteristic findings on MRI, which were seen in this case, include localization predominantly along the midline, infundibular thickening, isointense or hypointense signal on T1-weighted imaging, occasional cystic components, and variable intensity on T2-weighted imaging.[13] Elevation of the beta human chorionic gonadotropin level and, less commonly, of the alpha-fetoprotein level can occur in serum and CSF. In a retrospective case series involving patients with histologically confirmed CNS germ-cell tumors, 41% had elevated beta human chorionic gonadotropin levels in CSF, whereas 31% had elevated levels in serum.[14]

Treatment of CNS germinomas relies on conventional chemotherapy and radiation therapy and is primarily guided by evidence from retrospective case series and prospective observational studies.[15] Response rates are favorable; however, permanent neurologic disability is common, and these tumors can recur later in life.[15]

This case presented a diagnostic challenge, owing in large part to the nonspecific findings on initial presentation and the rarity of the final diagnosis. Although neither the discussant nor the treatment team suspected the presence of an intracranial germinoma, the development of diabetes insipidus led them to the pituitary stalk, where they were able to finally track down the diagnosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Solomon AJ, Naismith RT, Cross AH. Misdiagnosis of multiple sclerosis: impact of the 2017 McDonald criteria on clinical practice. Neurology 2019;92:26-33.
2. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler 2008;14:1157-74.
3. Helbok R, Broessner G, Pfausler B, Schmutzhard E. Chronic meningitis. J Neurol 2009;256:168-75.
4. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. Radiographics 2007;27:525-51.
5. Rigakos G, Liakou CI, Felipe N, Orkoulas-Razis D, Razis E. Clinical presentation, diagnosis, and radiological findings of neoplastic meningitis. Cancer Control 2017;24:9-21.
6. Turcu AF, Erickson BJ, Lin E, et al. Pituitary stalk lesions: the Mayo Clinic experience. J Clin Endocrinol Metab 2013;98:1812-8.
7. Freda PU, Post KD. Differential diagnosis of sellar masses. Endocrinol Metab Clin North Am 1999;28:81-117.
8. Gao Y, Jiang J, Liu Q. Extragonadal malignant germ cell tumors: a clinicopathological and immunohistochemical analysis of 48 cases at a single Chinese institution. Int J Clin Exp Pathol 2015;8:5650-7.
9. Birnbaum T, Pellkofer H, Buettner U. Intracranial germinoma clinically mimicking chronic progressive multiple sclerosis. J Neurol 2008;255:775-6.
10. Krolak-Salmon P, Androdias G, Honnorat J, et al. Beware of optic neuritis! Lancet Neurol 2002;1:516-7.
11. Suresh TN, Mahadevan A, Santosh V, Shankar SK. Subarachnoid spread of germinoma mimicking tuberculous meningitis. Neurol India 2004;52:251-3.
12. Guzzo MF, Bueno CB, Amancio TT, et al. An intrasellar germinoma with normal tumor marker concentrations mimicking primary lymphocytic hypophysitis. Arq Bras Endocrinol Metabol 2013;57:566-70.
13. Liang L, Korogi Y, Sugahara T, et al. MRI of intracranial germ-cell tumours. Neuroradiology 2002;44:382-8.
14. Takami H, Fukuoka K, Fukushima S, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neuro Oncol 2019;21:1565-77.
15. Osorio DS, Allen JC. Management of CNS germinoma. CNS Oncol 2015;4:273-9.