Clinical Reasoning: Vanishing tumor

A 7-year puzzle solved

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SECTION 1

In 2005, a 60-year-old man presented to the hospital complaining of a 2-month history of headaches and lethargy. His medical history included osteoarthritis and hypertension. From a social perspective, he was married with children, drove a truck for a living, and had never traveled abroad. His family history was unremarkable. Investigations included a brain CT, which highlighted an enhancing, space-occupying lesion in the left basal ganglia with associated edema and mass effect (figure, A). He was prescribed high-dose dexamethasone while awaiting a neurosurgical review. One week later, a prebiopsy, contrast-enhanced CT showed a reduction in the size of the caudate head mass (figure, B). MRI brain with gadolinium showed small white matter changes and no mass was evident. He did not proceed to biopsy and was subsequently observed. CSF analysis was abnormal, revealing mature, lymphoid cells and some larger immature cells, some of which appeared plasmacytoid (B cell). Although suspicious for

lymphoma, this result was nondiagnostic. The CSF protein level was 331. CSF low-density lipoprotein, Epstein-Barr virus, and flow cytometry were not performed. The β 2-microglobulin level and serum low-density lipoprotein were normal. Serology for cytomegalovirus and toxoplasma were negative, as were ELISA for *Toxocara* and HIV screen. Slit-lamp examination was unremarkable. He was discharged, but readmitted 2 weeks later with a deep vein thrombosis. Repeat CSF cytology was again nondiagnostic. CSF was not examined for oligoclonal bands or myelin basic protein. A bone marrow biopsy and staging CT had normal results. Whole body PET/CT was unavailable.

Questions for consideration:

1. What is the differential diagnosis for this case presentation?
2. Should steroids be used prior to biopsy of an enhancing CNS lesion?
3. How should this patient be followed?

GO TO SECTION 2

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Figure Neuroimaging series highlighting the initial radiologic abnormality that vanished and the recurrence 7 years later that led to the diagnosis of primary CNS lymphoma

(A) CT highlights a large, enhancing, space-occupying lesion in the left basal ganglia with associated edema and mass effect. (B) Image confirms a reduction in size of the caudate mass 1 week after initiation of steroid therapy. A complete radiologic response was observed on follow-up MRI brain (C.a [contrast] and C.b [fluid-attenuated inversion recovery]). (D) MRI brain performed following re-presentation with confusion and hallucinations was normal. (E) T1-weighted image postgadolinium confirms numerous foci of enhancement in the left temporal lobe. (F) Repeat MRI brain confirms progression of the left temporal lobe lesions suspicious for malignancy. (G) Following completion of 4 cycles of chemotherapy, a good radiologic response to treatment is evident on MRI brain.

SECTION 2

This case describes a vanishing tumor, an enhancing lesion that characteristically disappears spontaneously or reduces to less than 70% of the initial tumor volume observed radiologically before definitive diagnosis and treatment other than with steroids.¹ With respect to vanishing tumors seen within the CNS, the differential diagnosis includes primary CNS lymphoma (PCNSL), inflammatory conditions such as multiple sclerosis, acute disseminated encephalomyelitis or neurosarcoidosis, and cerebral infections (table).^{1,2} A vanishing tumor is estimated to occur in 1:60,000–1:100,000 patients with other cancers, including renal cell carcinoma and melanoma.¹

Ideally, glucocorticoid therapy should be avoided prior to biopsy of a lesion that has neuroradiologic characteristics suspicious of PCNSL, as this may prevent histologic confirmation of the diagnosis. With glucocorticoid therapy, complete tumor cell eradication is never achieved and PCNSL inevitably recurs, facilitating the delayed histologic diagnosis.¹

However, there are no guidelines available to help determine the appropriate method or duration of follow-up. MRI brain surveillance for a period of 5 years has been suggested.¹ This duration is proposed on the basis of a case of PCNSL that entered complete remission for 5 years following glucocorticoid therapy.² Until now, there has not been a case of vanishing PCNSL reported to recur more than 5 years following initial remission induced by glucocorticoid therapy.

One year later, our patient underwent CT and MRI brain, which confirmed a complete radiologic remission of the tumor (figure, C.a and C.b). Lumbar puncture and CSF cytologic assessment was performed 6 times and were all nondiagnostic. The patient did not attend for further follow-up. In December 2011, he re-presented with confusion, impaired hearing, and hallucinations. Repeat CT and MRI brain were unremarkable (figure, D). CSF analysis revealed pleocytosis, an atypical finding, suspicious of lymphoma. In May 2012, he attended with

Table Vanishing tumors seen within the CNS			
Differential diagnosis	Presentation	Features on CT	Features on MRI
Secondary CNS lymphoma	Asymptomatic; motor weakness; sensory symptoms; seizures	2/3 Leptomeningeal involvement, 1/3 parenchymal lesion	Gd: modality of choice, enhancement of leptomeninges, dura, cranial nerves
Primary CNS lymphoma	M:F 2:1; >50 y; symptoms: short duration, <3 mo; risk factors: HIV, post-transplant, IgA deficiency; symptoms: ↑ ICP, focal neurologic deficits, seizures	Supratentorial (75%-85%); solitary or multiple masses (hyperattenuating [70%]), enhancing, limited mass effect for size, limited surrounding edema	T1: hypointense to white matter; T1C + Gd: high-grade tumors, homogenous enhancement (thick peripherally); low-grade tumors: absent to moderate enhancement; T2: variable intensity; DWI: restricted diffusion; PI: modest increase in CBV; spectroscopy: large choline peak, reversed choline: creatinine ratio
Cerebral toxoplasmosis	Immunocompromised, e.g., HIV/transplant recipient; vague symptoms	Multiple hypodense lesions; location: basal ganglia or corticomedullary junction; postcontrast: smooth ring enhancement	T1: difficult to identify; T2: perilesional edema; variable intensity: hyperintense, necrotizing encephalitis isointense: abscess; T1 + Gd: nodular/ring enhancement
GBM	Focal neurologic deficit, Symptoms: ↑ ICP, seizures	Irregular heterogeneously enhancing margins, central necrosis, mass effect, surrounding vasogenic edema; butterfly glioma: involves contralateral hemisphere; multifocal (20%)	PI: CBV elevated; DWI: no diffusion restriction; spectroscopy: choline ↑, lactate ↑, lipids ↑, NAA ↓, myo-Inositol ↓
Tumefactive demyelinating lesion	F > M; young-middle age; not postinfective; symptoms (atypical for multiple sclerosis): focal neurologic deficits, seizures, aphasia	Large (>2 cm), solitary, ill-defined, incomplete leading edge, ring-enhancing lesion; central necrosis; perilesional edema; minimal mass effect	T1 + Gd: contrast enhancement (open ring), 50%; PI: mean relative cerebral blood volume: less than gliomas and lymphoma; DWI: increase in ADC
ADEM	Recent viral infection or vaccination, typically children and adolescents, CSF: MBP ↑	Small punctate low-density lesions, bilateral and asymmetrical within white matter, ± ring enhancement	T2: regions of high signal and edema; T1C + Gd: ± enhancement; DWI: peripheral restricted diffusion
MS	Variable presentation: relapsing and remitting (70%), secondary or primary progressive (10%); symptoms: sensory, motor, or mixed; lesions disseminated in time and space	Nonspecific	T1: plaques: isointense to-hypointense (chronic); T2: plaques: hyperintense; FLAIR: plaques: hyperintense; T1C + Gd: enhancement (active plaques); DWI: active plaques: restricted diffusion; spectroscopy: NAA ↓ within plaques
Cerebral abscess	↑ ICP, seizures, focal neurologic deficits; risk factors: systemic sepsis, dental abscess, bacterial endocarditis	Similar features to MRI, uniformly rim enhancing lesion with thickened capsule and diminished hypodense central cavity	T1: central low intensity, peripheral low intensity (edema), ring enhancement; T2/FLAIR: central high intensity, peripheral high intensity, abscess capsule-low signal thin rim; DWI: central restricted diffusion; PI: CBV ↓ in surrounding edema; spectroscopy: succinate ↑, lactate ↑, NAA ↓
Neurosarcoidosis	↑ ICP, CNPs, DI, seizures, motor/sensory neuropathy, myelopathy; isolated neurosarcoidosis: rare	False-negative CT 60%; hydrocephalus	T1C + homogenous enhancement

Abbreviations: ADC = apparent diffusion coefficient; ADEM = acute disseminated encephalomyelitis; CBV = cerebral blood volume; CNP = cranial nerve palsy; DI = diabetes insipidus; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; GBM = glioblastoma multiforme; Gd = gadolinium; ICP = intracranial pressure; IgA = immunoglobulin A; MBP = myelin basic protein; MS = multiple sclerosis; PI = perfusion imaging.

chest pain. A pulmonary embolus (PE) was identified on CT pulmonary angiography. Another MRI brain was performed, which showed numerous foci of enhancement in the left temporal lobe on T1-weighted images taken postgadolinium, suspicious for malignancy (figure, E). His symptom profile evolved. He developed memory loss, complex partial seizures, and ataxia. MRI showed evidence

of progression of disease (figure, F). Biopsy of the temporal lobe lesion confirmed non-Hodgkin, diffuse, large B-cell lymphoma. Staging CT ruled out systemic lymphoma, confirming PCNSL. PET/CT was again unavailable.

Question for consideration:

1. What is the management of PCNSL?

GO TO SECTION 3

SECTION 3

The optimal treatment of PCNSL is uncertain and clinical trials should always be considered. Surgical intervention is limited to stereotactic biopsy to make a tissue diagnosis, but may be considered in the setting of impending increased risk of herniation, hydrocephalus, and uncontrolled mass effect. Surgical resection can induce neurologic deficits, can delay treatment, and does not confer a survival benefit.³

For patients with a good performance status, combination chemotherapy is the mainstay of treatment. A combination regimen of high-dose methotrexate (HDMTX) with cytarabine has been shown to improve overall and complete response (CR) rates compared to methotrexate alone.³

The majority of PCNSL (~95%) express CD20.⁴ A therapeutic effect of rituximab, a chimeric, monoclonal anti-CD20 antibody, has been suggested. Recently, 2 retrospective, observational studies reported improved rates of CR with the addition of rituximab to HDMTX-containing regimens (100% vs 68.4%, $p = 0.02^4$; 70% vs 36%, $p = 0.01^5$). One of these studies also reported improved survival data on the addition of rituximab to HDMTX compared to HDMTX alone (median progression-free survival was 26.7 months vs 4.5 months, $p = 0.003$; median overall survival was 16.3 months in the HDMTX alone group and has not been reached in the HDMTX/rituximab group, $p = 0.01$).⁵ Although the level of evidence supporting the use of rituximab for treatment of PCNSL is low, its use is encouraged. Two randomized trials currently underway are attempting to establish the exact role of rituximab in the management of PCNSL (NCT01011920; NTR2427).³

Radiotherapy was the initial treatment of choice prior to studies of HDMTX, which showed superior survival rates over radiotherapy alone. PCNSL is

sensitive to radiotherapy and this remains a palliative treatment option.³ Inclusion of the whole brain and eyes in the radiotherapy field is recommended because of the diffuse infiltrative nature of PCNSL. Consolidation, after HDMTX-based chemotherapy, represents the best role for radiotherapy in the management of PCNSL. It is associated with risk for neurotoxicity, with a cumulative 25%–35% incidence at 5 years and related 30% mortality.^{3,6} Consolidation radiotherapy is particularly challenging in patients aged ≥ 65 years and radiotherapy is often deferred until disease progression.³ Similarly, in patients who achieve CR to chemotherapy, deferring whole-brain radiotherapy (WBRT) until potential relapse has been proposed in an effort to minimize the neurotoxicity risk. However, this strategy requires validation in randomized trials.⁶ In contrast, consolidation radiotherapy is unavoidable in those with residual disease after chemotherapy.³ The optimal dose of WBRT is controversial. A dose of 40–50 Gy is recommended.³ Some studies suggest equivalent efficacy and better tolerability when the dose of WBRT is reduced to 23–30 Gy in patients with CR after chemotherapy.^{6,7}

Systemic chemotherapy (HDMTX/cytarabine) and rituximab was chosen in the case presented. After 4 cycles of treatment, repeat MRI confirmed a good response (figure, G). The treatment course was complicated by febrile neutropenia and recurrent PE. On completion of treatment, active surveillance was undertaken, as opposed to consolidation radiotherapy.

Question for consideration:

1. Is there a known association between venothromboembolism (VTE) and PCNSL?

GO TO SECTION 4

SECTION 4

The association between malignancy and thrombosis is well-recognized and occurs in 15% of all cancer patients.⁸ The risk of VTE in the setting of a brain tumor is high, affecting 28% of patients with malignant gliomas.⁸ Predisposing risk factors other than the inherent risk of malignancy include the presence of leg paresis, histologic diagnosis of glioblastoma multiforme, age ≥ 60 years, large tumor size, and use of chemotherapy. One study found an incidence of VTE of 60% (25/42) in patients with PCNSL. Almost all events occurred in the first 3 months of treatment.⁸

DISCUSSION A vanishing tumor is a complex diagnostic dilemma and is not specific for one disease. The clinical course of a vanishing tumor, with the exception of PCNSL, has not been completely described. In the case of PCNSL, the diagnosis is made at the time of recurrence. Literature suggests that surveillance of a vanishing tumor should take the form of regular MRI for a duration of 5 years. However, in the case presented, the vanishing tumor remained in complete remission for a 7-year period with steroid treatment alone, at which point it recurred and was definitively diagnosed as a PCNSL.

A similar case reported symptomatic recurrence after 5 years in remission, which led to the radiologic diagnosis of recurrence.² Relapse generally occurs within 18 months in 80% of patients with PCNSL vanishing tumors, with a median remission duration of 7 months for PCNSL (range 1–54 months).⁹ Late recurrence (≥ 5 years from initial diagnosis) in appropriately treated PCNSL is a rare event. One large series identified a late relapse rate of 4% in patients who achieved CR following appropriate treatment.¹⁰ The median time to first relapse was 7.4 years (range 5.2–14.6 years).¹⁰ Sustained clinical follow-up is therefore recommended given the incidence of late recurrence as demonstrated by this case and those reported in literature.

AUTHOR CONTRIBUTIONS

Ciara Kelly: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Sean O'Dowd: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Catherine Drake: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, contribution of vital reagents/tools/patients. Lauragh McCarthy: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Niamh

Bermingham: analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Noel Fanning: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Sean O'Sullivan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Seamus O'Reilly: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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