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Long-term follow-up of vanishing tumors in the brain: How should a lesion mimicking primary CNS lymphoma be managed?

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ABSTRACT

Objectives: The spontaneous disappearance of a tumor is referred to as a vanishing tumor. Most vanishing tumors in the brain are eventually diagnosed as malignant tumors or multiple sclerosis. However, their long-term clinical course remains unclear. This study aims to elucidate the management of vanishing tumors in the brain.
Patients and methods: We defined a vanishing tumor as a case in which the tumor spontaneously disappeared or decreased to less than 70% of the initial tumor volume before definitive diagnosis and treatment (other than steroid treatment). Ten cases of vanishing tumors are reviewed.
Results: Nine patients underwent biopsy at least once. Five patients, all of whom had malignant tumors (primary central nervous system lymphoma: 4, germinoma: 1) that recurred in 4–45 months (median: 7 months), underwent a second biopsy after the reappearance of the tumors. Five patients (tumefactive demyelinating lesion: 1, undiagnosed: 4) who had no relapse are alive, and their median follow-up time is 44 months. No cases have yet been reported of malignant brain tumors that recurred more than 5 years after spontaneous regression.
Conclusions: Patients with vanishing tumors should be followed up carefully by magnetic resonance imaging for at least 5 years, even after the disappearance of an enhancing lesion.

1. Introduction

Spontaneous regression of a malignant tumor is highly unusual, but this phenomenon is encountered on some occasions. These spontaneously disappearing, enhancing lesions are observed by magnetic resonance imaging (MRI) or computed tomography (CT). This clinical condition is referred to as a vanishing tumor, tumor regression, ghost tumor, or burned-out tumor [1–3]. It is estimated that this phenomenon may occur in 1:60,000–1:100,000 patients with cancer; this phenomenon has been observed in renal cell carcinomas, neuroblastomas, malignant melanomas, and germ cell tumors of the testes [1,4]. Most vanishing tumors in the central nervous system are eventually diagnosed as primary central nervous system lymphoma (PCNSL) [1–3,5] or as a demyelinating disease such as multiple sclerosis (MS) [1,6]. This unusual clinical phenomenon presents diagnostic difficulties and thus leads to confusion in determining treatment options. Occasionally, it may be difficult to distinguish between malignant tumors, such as PCNSL, and many other central nervous system diseases by using clinical, radiological, and laboratory findings, and a biopsy is therefore necessary for definitive diagnosis. However, when a first biopsy is performed and the pathological findings show only nonspecific lymphocyte inflammatory changes with or without demyelination, it is very difficult to identify the cause of these inflammatory changes. Repeated biopsies at the time of tumor recurrence are sometimes necessary for the diagnosis of PCNSL [6].

This study addresses the management of a lesion that mimics primary CNS lymphoma with spontaneous radiological improvement and inconclusive biopsies of the brain. This phenomenon represents a recurrent problem in daily practice and has not yet been addressed in depth in the literature. Here, we report 10 cases of vanishing tumors and clarify the treatment and follow-up of the vanishing tumors after lesion disappearance. We also estimated histological confirmation of demyelination in undiagnosed cases.

2. Materials and methods

A vanishing tumor is defined as a case in which there is a strong suspicion of brain tumor from the clinical history and in which there

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Table 1
Characteristics of patients with vanishing tumor.

Case No.	Diagnosis	Age (years)	Sex	Lesion	Location	Presentation	CSF cell count at onset (μl)	CSF protein concentration at onset (mg/dl)	CSF cytology
1	PCNSL	70	F	Multiple	L frontal, L cerebellum	Gait disturbance	ND	ND	ND
2	PCNSL	25	M	Multiple	Cerebellum, cerebellar peduncle	Diplopia	ND	ND	ND
3	PCNSL	64	M	Single	Cerebellum	Diplopia	ND	ND	ND
4	PCNSL	49	F	Single	Cerebellum	Gait disturbance, diplopia	22	77	Class 3
5	Germinoma	36	M	Multiple	L thalamus, midbrain	L hemiparesis, diplopia	2	45	Class 2
6	TDL	59	M	Single	L parietal	L hemiparesis, numbness	48	110	Class 2
7	Undiagnosed	65	F	Single	R cerebellar peduncle	L facial dysesthesia	<1	33	Class 2
8	Undiagnosed	26	M	Single	L frontal	Focal seizure	5	70	ND
9	Undiagnosed	42	M	Single	L frontal	Headache	59	59	Class 2
10	Undiagnosed	64	M	Multiple	L parieto-occipital, lumber spinal cord	Aphasia	19	46	Class 2

M, male; F, female; R, right; L, left; CSF, cerebrospinal fluid; ND, not done; PCNSL, primary central nervous system lymphoma; TDL, tumefactive demyelinating lesion.

are gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) enhancing lesions on initial MRI that spontaneously disappear or decrease to less than 70% of the initial tumor volume before a definitive diagnosis and treatment, other than steroid treatment, for more than 3 months. From January 2000 to December 2010, clinical charts and radiological examination results of 10 patients who presented to the National Cancer Center Hospital with an enhancing lesion on MRI and in whom the lesion regressed or disappeared without treatment (other than steroid treatment) were reviewed. The internal review board of the National Cancer Center Hospital approved this study.

3. Results

3.1. Patient characteristics

Ten patients who exhibited a spontaneously disappearing or decreased mass lesion from 2000 to 2010 and who met our criteria for a vanishing tumor were selected. Clinical and radiological features of these 10 patients are summarized in Tables 1 and 2. The follow-up time ranged from 19 to 96 months (median: 50 months). The age of the patients ranged from 25 to 70 years (median: 54 years).

Definitive diagnoses were made in 6 of the 10 patients. Of these 6 patients, 4 had PCNSL (40.0%), 1 had germinoma (10.0%), and 1 had tumefactive demyelinating lesion (TDL) (10.0%). Definitive diagnoses could not be made in the case of 3 patients who showed inflammatory changes without demyelination (30.0%); moreover, in 1 patient, the tumor spontaneously disappeared without biopsy (10%). Of the 5 patients who relapsed, 2 patients with diffuse large B-cell lymphoma (PCNSL) (cases 3 and 4) and 1 patient with germinoma (case 5) are still alive, and their median follow-up time is 59 months. The remaining 2 patients who were diagnosed with PCNSL (cases 1 and 2) died after 13 and 6 months from their first biopsy, respectively. Five patients (cases 6–10), diagnosed with TDL or undiagnosed, had no relapse and are alive; their median follow-up time is 44 months.

3.2. Initial clinical symptoms at onset

The 5 patients who were ultimately diagnosed with malignant tumors complained of gait disturbance (2), diplopia (2), and hemiparesis (1). Another 5 patients with TDL and the undiagnosed case complained of seizure (1), headache (1), hemiparesis (1), sensory disturbances (1), and aphasia (1). All patients were gradually aware of these symptoms, except for seizure; therefore, acute cerebrovascular disease was excluded and tumor was suspected. None of the patients showed symptoms of complications caused by viral infection, such as fever, cough, or skin rash.

3.3. Radiological changes and steroid use

Four patients (cases 1, 2, 5, and 10) showed multiple enhancing lesions on MRI. Eight patients began treatment with steroids in another hospital. Enhancing lesions in 7 patients (70%) completely disappeared at least once, and 6 of these patients were treated with steroids. Five patients diagnosed with TDL and the undiagnosed patient showed no recurrence for the median follow-up time of 44 months (range: 34–96 months). In 3 patients (cases 1, 4, and 5) with malignant tumors, enhancing lesions were decreased to 7.2%, 10.9%, and 28.5% of the initial tumor volume, respectively; these cases relapsed after 7, 4, and 6 months from onset, respectively. In the other 2 cases (cases 2 and 3) with tumors, the initial enhancing lesions disappeared after 1.2 and 0.8 months, respectively, and complete remission lasted for 14 and 45 months, respectively.

3.4. Cerebrospinal fluid and pathological findings

Seven patients underwent cerebrospinal fluid (CSF) examination, and 2 patients (including 1 patient with germinoma) had results within normal limits. The other 5 patients (including 1 patient with PCNSL) showed increased number of cells and increased protein levels. Malignant cells were not detected in the CSF cytology except case 8 who did not underwent CSF cytology.

Nine patients underwent 1 or more biopsies by stereotactic needle biopsy or open surgery, and the removal of all the lesions targeted by biopsy was confirmed by intraoperative navigation system and postoperative MRI. Only 1 tumor (case 7) spontaneously disappeared without biopsy.

Pathological findings in 7 patients (cases 1–3, 6, and 8–10) showed nonspecific lymphocyte inflammatory changes at the first biopsy. Four patients with PCNSL underwent biopsy twice. The first pathological findings in 4 patients showed only nonspecific lymphocytes, and 2 patients (50%) were treated with steroids before