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Letter to the Editor

Vanishing midbrain mass lesion - A germinoma?

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1. Introduction

The clinical phenomenon of a spontaneous disappearance of an enhancing lesion on cerebral computed tomography (CCT) or magnetic resonance imaging with gadolinium (MRI) is referred to as a vanishing tumor [1]. This is a phenomenon observed in 1:60.000–1:100.000 cancer patients. [2] The differential diagnoses include primary central nervous system lymphoma (PCNSL), demyelinating disease, glioma with spontaneous regression, inflammatory disease, such as sarcoidosis, Behcets disease/angiitis with granoulomatosis and parasitic disease. The vanishing tumor phenomenon has also been reported in solid tumors, such as melanoma, renal cell carcinoma, neuroblastoma and germ cell tumors of the testes [1,3], as well as in rare cases of intracranial germ cell tumors (iGCT).

Detailed studies on the immunological mechanisms and the composition of immune infiltrates in these entities are rare [3–6].

Early and extensive workup and surgical evaluation with subsequent immuno-histopathological diagnosis are obligatory, since timely therapy can improve the clinical outcome significantly [7].

We here present an unusual case of an 18-year-old male with a vanishing midbrain mass lesion. The differential diagnoses are discussed, and we provide a review on the current literature.

2. Methods

2.1. Illustrative case

2.1.1. Initial presentation

An 18-year-old male student with a history of childhood bronchial asthma presented to the emergency room with hemicranial throbbing headache and vomiting. A clinical examination revealed no focal neurological deficits. Cerebral MRI showed a 1.2 × 1.9 × 1.3 cm midbrain mass lesion with cystic components and a homogenous contrast enhancement, as well as signs of hydrocephalus with III-ventricle enlargement. (Fig. 1a-A).

Initial therapy included 3 days of administration i.v. corticosteroids (dexamethasone 40 mg per day), 250 ml mannitol 15% (once), and an endoscopic ventriculostomy, which relieved the hydrocephalus and allowed to obtain ventricular cerebrospinal fluid (CSF). Histology of the ventricular CSF revealed glial fragments in a fibrillary matrix without any signs of malignant cells. A tentative diagnosis of tectal glioma was made, and the treating physician because of the delicate location of the abnormality suggested a watch- and- wait policy.

2.1.2. Clinical course

Over the following ten months, due to the involvement of the anatomical structures in the midbrain patient gradually developed a bilateral external oculomotor nerve palsy and a right cranial nerve IV palsy. Other aetiologies for ophthalmoplegia such as Grave's disease and myasthenia gravis have been excluded. Several eye alignment surgeries were performed in order to ameliorate the extent of diplopia. Success was only limited.

In 6/2013 the patient developed a Parinaud syndrome, and corresponding cMRI demonstrated a progressing contrast-enhancing midbrain lesion. No further ophthalmologic intervention was done. Over the subsequent course of 7 months, however, this lesion started to shrink again without any specific treatment. Two years after the onset of the disease, the volume was reduced by > 70%, and only minimal inhomogeneous gadolinium enhancement was still present (Fig. 1b-B).

Two and a half years after initial MRI, the patient experienced again a progressive neurological deterioration with gait disturbance, dysarthria and dizziness. The midbrain lesion on MRI had recurred in 6/14 (Fig. 1C). Extensive workup, including FDOPA-PET, studies of the cerebrospinal fluid (CSF), CT-staging, MRI-spectroscopy, hormone testing, laboratory work-up, including virological status, and the search for other infectious agents (fungi, mycobacterial infection, atypical infectious agents such as toxoplasmosis) were unrevealing. A Klinefelter genotype associated with germ cell tumors was excluded by genetic analysis. Urological examination excluded a gonadal pathology. Due to the localization of the lesion, no consent for a biopsy could be obtained at this time. Although a neoplasm was still considered, we decided in favour of a therapeutic attempt with immunosuppressive therapy consisting of steroids followed by azathioprine on the assumption of a granulomatous inflammatory systemic disease, such as sarcoidosis. MRI scan was not suggestive of PCNS-lymphoma. After short term (5 months) clinical stabilization and radiological regression of the lesion, clinical symptoms started to progress again, and MRI changes also started to involve the right thalamus (Fig. 1D). At that time, the patient underwent an MRI guided stereotactic biopsy with three tissue samples collected in the thalamic region at two distinct sites 5 mm apart.

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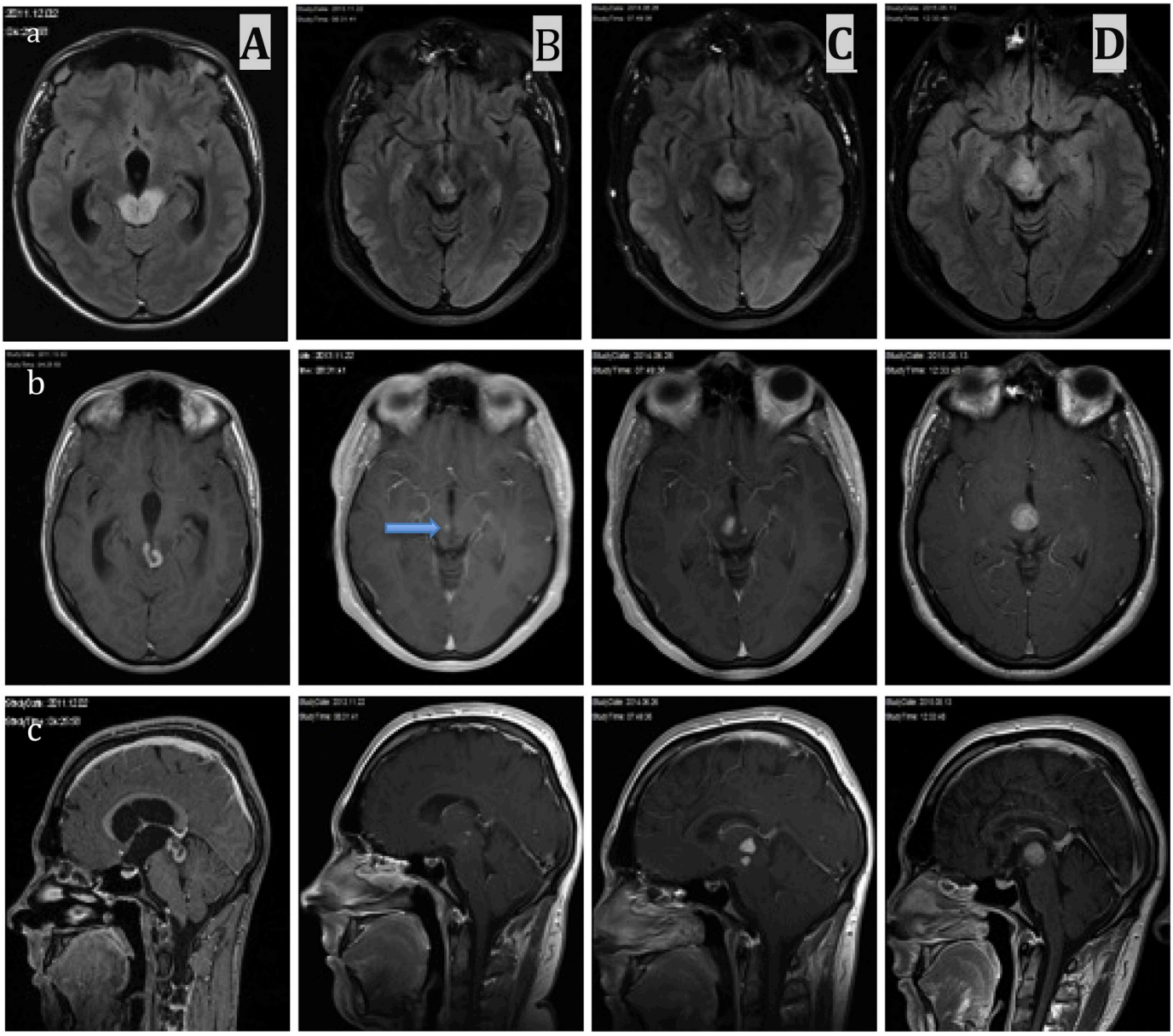

Fig. 1. Consecutive FLAIR (a) and T1- weighted magnetic resonance images with gadolinium (b: axial plane; c: sagittal plane) showing evolution of the MRI changes over time. A. Initial MRI revealed a 1 × 2 × 1.5 cm midbrain mass lesion with cystic component and homogenous gadolinium enhancement. There were also signs of occluding hydrocephalus at that time. B. The lesion almost disappeared (> 70% mass reduction) spontaneously without any treatment 2 years after initial presentation (arrow b-B). C. 7 months after regression (6/2014), marked enlargement of the midbrain mass was seen again and correlated with clinical deterioration. New gadolinium enhancing lesion in the thalamus appeared 3 years after the first clinical symptom. It was accessible for a biopsy while the original mass lesion had diminished in size again. The areas of increased T2 signal on FLAIR demonstrated only in a small circumscribed area facilitated diffusion in the ADC (data not shown).

2.2. Immunohistochemistry

The tissue was fixed in 4% buffered formalin overnight and embedded in paraffin. Sections (5 µm) cut from all paraffin blocks were used for standard and immunostaining.

Based on histopathology and immunohistochemistry, germinoma with extensive granulomatous inflammation was diagnosed. No components of embryonal carcinoma, yolk sac tumor, or choriocarcinoma were detected (Fig. 2).

Rapid tumor-specific radiation therapy of the supratentorial tumor and the adjacent ventricle system was initiated, which led to a significant clinical improvement. However, the patient never reached his baseline neurological condition.

3. Discussion

Spontaneously vanishing lesions of the CNS do not suggest a priori a neoplasm but rather an inflammatory or immune-mediated process.

The case of an extragonadal, intracerebral germinoma presented here highlights such a pitfall. Table 1 lists the MRI characteristics of the most likely differential diagnoses of a vanishing midline mesencephalic mass lesion.

Germ cell tumors (GCT) rarely occur in extragonadal sites and often involve the midline structures not only in the brain but also in the mediastinum and sacrococcygeal region. Intracerebral germinomas may occur in the pineal and suprasellar region, thalamus, basal ganglia, intraventricularly, medulla oblongata, optic nerve, cerebellopontine angle and corpus callosum or spinal cord [4]. In up to 30% of the cases,

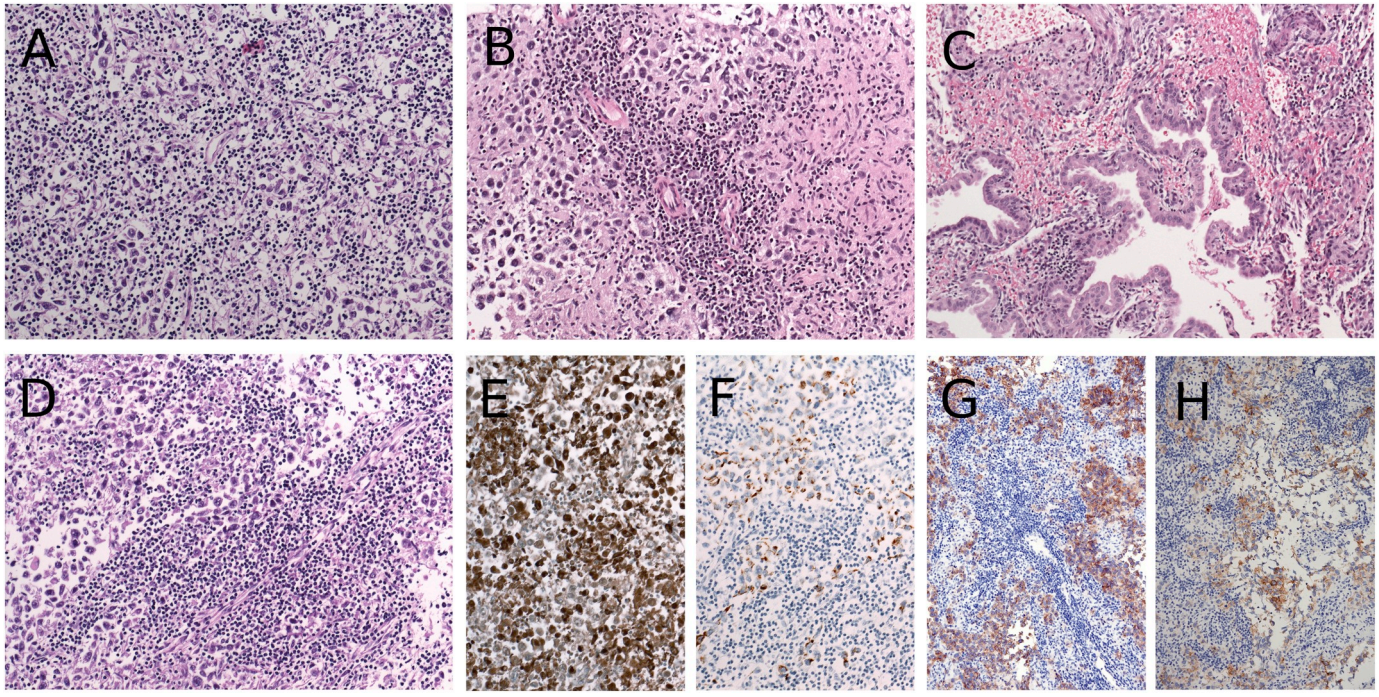

Fig. 2. H&E histology of dense lymphocytic ($CD3^+$, $CD4^+$, CD 20^-) infiltrated tissue with scattered large undifferentiated tumor cells (A and D). Foci of granulomatoid inflammation with epitheloid cells (B) and chronic inflammatory infiltrates in a cross section of ependyma (C) but no components of a mixed germ cell tumor. Pronounced response of CD68+ histiocytes/macrophages (E). Weak cytokeratin positivity of tumor cells (F). Tumor cells expressing c-kit (G) and PLAP (H).

germinomas can also occur with bifocal localization in the pineal and suprasellar region without metastases elsewhere. The predilection for these anatomical structures has mainly been attributed to aberrant neurodevelopmental pathways, such as ectopic migrational stop of the undifferentiated primordial cells in the midline during early stage of the rostral neural tube enfolding [5]. The prevalence of primary GCT is much higher in Asian than in Western countries. Illustrative cases of midbrain involvement found in the literature are summarized in Table 2.

Clinical symptoms may develop early even in small tumors mainly due to a mass effect on the surrounding anatomical structures.

A retrospective clinical study by Gao et al. [3] found that hydrocephalus (82.4%) and diplopia (46.7%) were the most common clinical presentations in a cohort of 34 patients with CNS germinoma. Like our patient, most intracranial germinoma patients are between 15 and 29 years old (mean 24 years) and male.

In our patient, spontaneous regression of the lesion without treatment was initially an indication of an inflammatory aetiology. This, however, also applies to viral infections, cerebral lymphoma, autoimmune processes, and to NMDA receptor encephalitis in rare cases. The previously coined term was idiopathic inflammatory changes in the brain.

It is also accepted that a malignant tumor may evolve from these changes over time [8].

Long lasting spontaneous regression, as seen in our patient over 7 months without any treatment, is very unusual. To the best of knowledge, such a case has not yet been reported in the literature.

The transient regression of a neoplasm after steroid treatment, as seen in our patient after the first regrowth of the lesion, is less surprising [9], and has been attributed to the impact of such medication on diffuse lymphocytic infiltration. Likewise, spontaneous regression of the germinoma is also probably a consequence of the abating intense lymphocytic reaction [10], which is thought to occur initially in a protective attempt.

Table 1
MRI characteristics of the most likely differential diagnoses of a vanishing midbrain tumor.

	T1	T2	T1 + C (Gd)
Primary CNS Lymphoma	Hypointense	Iso/hyperintense	Ring enhancement in high grade tumors
Tectal Glioma	Iso- to slightly hypointense	Hyperintense	No or minimal
Sarcoidosis	Iso- or hypointense	Variable, most hyperintense	Homogenous
Tuberculoma	Isointense	Isointense, Perilesional gross vasogenic oedema	Ring enhancement
Toxoplasmosis	Iso- to hypointense	Hyperintense to isointense	Ring enhancing or nodular
MS	Iso- to hypointense	Hyperintense	Active lesions enhance (open ring sign)
Germinoma	Isointense or slightly hyperintense to adjacent brain	Isointense or slightly hyperintense to adjacent brain May have areas of cyst formation May have areas of haemorrhage (low signal) Have a predilection for invading adjacent brain (oedema) Central calcification appears low signal (engulfed pineal gland)	Vivid and homogenous

Table 2
Illustrative germinoma cases with midbrain involvement (literature)

Alter	Age/Sex	Localisation	Biopsy	Therapy	Outcome
Matsumoto et al. [11]	27/M	Left midbrain	MRI guided stereotactic	Radiotherapy	Alive at 1 month
Uchino et al. [12]	22/M	Left- midbrain-thalamus	Neuroendoscopic	Chemo- with radiotherapy	Alive at 6 months
Koizumi et al. [1]	29/M	Left-midbrain-Pons	MRI guided stereotactic	Chemo- with radiotherapy	Alive at 7 months
Strowd [13]	26/M	Left-midbrain- thalamus	MRI guided stereotactic	Chemo- with radiotherapy	
Maruya et al. [14]	29/M	Left-midbrain-thalamus	Open biopsy	Chemo- with radiotherapy	Alive at 5 years
Present case	18/M	Whole midbrain-thalamus	MRI guided stereotactic	Radiotherapy	Alive at 8 years

Prognosis of iGCTs is highly dependent on the histological subtype.

The gold standard is craniospinal radiotherapy in disseminated disease plus boost in the tumor region. It should be initiated as soon as possible after diagnosis. Our patient with localized intracranial disease underwent radiotherapy of the whole ventricle and tumor bed 24 Gy plus a boost to tumor bed 16 Gy. Total dose to tumor bed of 40 Gy was applied.

A five-year survival rate of 94.4% was reported by Gao et al. [3].

Due to the possibility of a vanishing tumor to re-occur, Okita et al. recommend a careful follow up for up to 5 years.

Our patient is still alive 8 years after initial symptoms. Four years after tumor-specific therapy he shows a stable neurological disease with permanent neurological deficits such as bilateral complete oculomotor palsy, deficits in horizontal and vertical gaze, intermittent diplopia, dysarthria, bilateral limb and gaith ataxia, however no sensorimotor deficits. These deficits could potentially be ameliorated by an earlier initiation of tumor-specific treatment.

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