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Short clinical case

A case of brain metastasis of a thymic carcinoma with a review of the literature

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ABSTRACT

Thymic epithelial tumors (TET) are rare lesions. The brain metastases of these tumors are even rarer. We report a case of brain metastases in a known patient with a thymic carcinoma diagnosed in October 2016. She was a 73-year-old woman who presented with headache, nausea, and right hemiplegia. Brain MRI revealed five lesions (1 insular, 1 frontal and 2 left temporal, 1 right parafalcine). These lesions were initially treated using two stereotactic radiosurgery gamma knives. A macroscopically complete excision of the left frontal lesion was subsequently performed without any complications with a good evolution of the neurological symptoms postoperatively. Immunohistochemical examination was compatible with metastatic thymic carcinoma. The patient died 14 months after the initial diagnosis. A review of the literature in English has reported another 45 TET cases with brain metastases.

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1. Introduction

Thymic epithelial tumors (TETs), grouping thymomas and thymic carcinomas, are rare tumors. Their annual incidence is about 0.15/100,000 people [1]. Despite aggressive local treatment, patients with thymoma or thymic carcinoma tend to relapse to distant sites; including regional lymph nodes, bones, liver and lungs. Brain metastases are rarely observed in thymic malignancies [2,3]. A review of the literature in English has reported another 45 TET cases with brain metastases. We report a case of thymic carcinoma with brain metastases and review the literature on cerebral metastases of thymoma and thymic carcinoma.

2. Observation

A 73-year-old woman diagnosed in October 2016 with Masaoka stage IVa sarcomatoid thymic carcinoma involving the pleura, lung, pericardium and bones. She was treated with 4 courses of CAP (Carboplatin-Taxol) chemotherapy and an enlarged monobloc resection (left Hemi-sternum + thymic mass + innominate venous trunk + left superior lobectomy + internal 1/3 of the clavicle + anterior arches of the 1st, 2nd and 3rd ribs). Postoperatively, adjuvant mediastinal closure radiotherapy was performed. The reassessment report showed a globally responsive disease, and cerebral magnetic resonance imaging (MRI) confirmed that there was a cerebral metastatic disease, with a left superior frontal cortical lesion of 18 mm, accompanied by peri-lesional edema and an left insular lesion of 9 mm (Fig. 1A–B–E).

Gamma knife stereotactic radiosurgery treatment of these 2 lesions was performed in February 2017. At the periphery of these lesions doses of between 22 and 23 Gy were delivered. The brain MRI of June 2017 confirmed these brain lesions known to be located primarily as follows: left insular measured at 7 mm against 9 previously; left frontal cortical lesion measured at 15 mm against 18 previously; a clear decrease of the peri-lesional edema ranges around these two lesions. In contrast, the appearance of new lesions, namely: 13 mm parafalcine nodular contrast enhancement in contact with the roof of the right lateral ventricle and 13 mm external left temporal on contrast enhancement. There exists around these two lesions a range of peri-lesional edema (Fig. 1E).

A second gamma knife stereotactic radiosurgery treatment of these 4 lesions was performed in July 2017. The cerebral MRI of August 2017 showed the four lesions previously described: left external temporal lesion measuring 15 mm against 13 mm; left frontal cortical lesion measuring 19 mm versus 15 mm previously; right parafalcinelesion of 17 mm as compared to 13 mm previously; left insular lesion measuring 7 mm stable. Appearance of a new left temporal cortical lesion measuring 5 mm (Fig. 1E). The sequential management of the different brain lesions was represented in Table 1.

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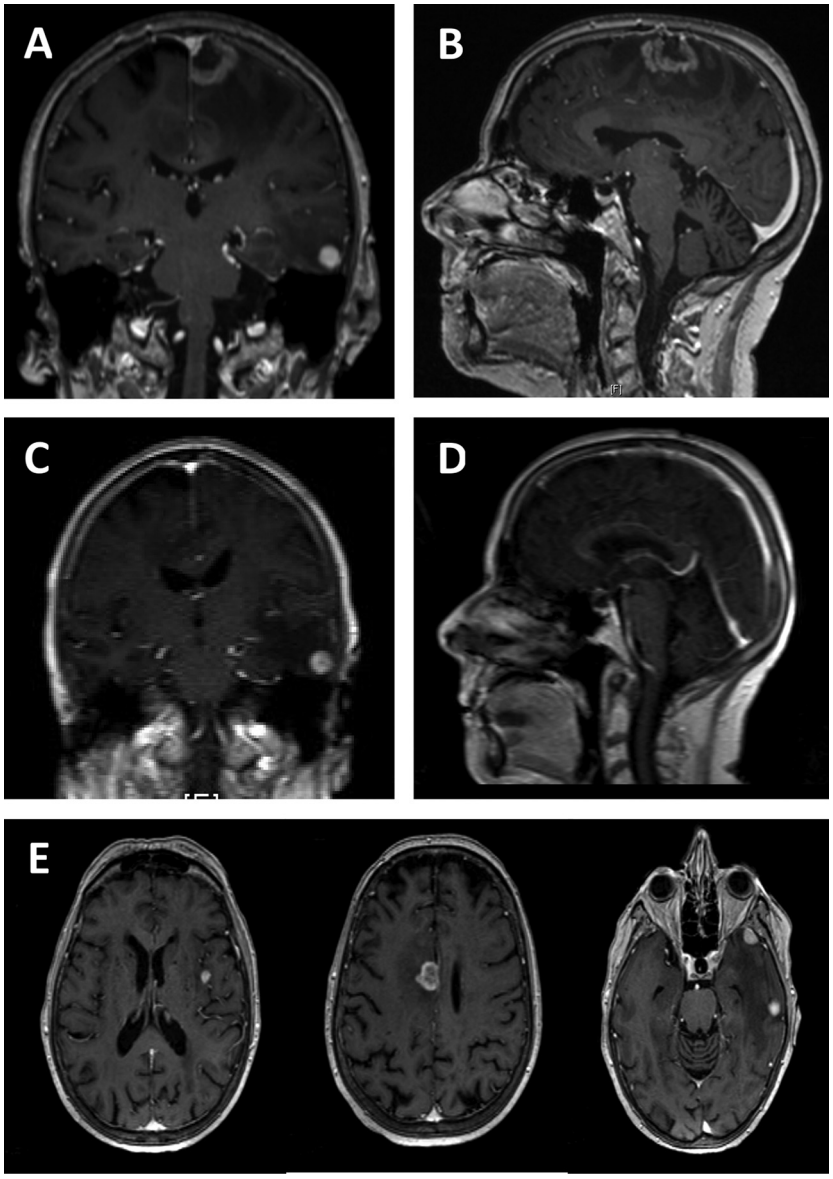

Fig. 1. Preoperative T1 gadolinium-enhanced coronal (A) and sagittal (B) images of the metastatic thymic carcinoma, demonstrating a heterogeneous enhancement pattern and the dural-based appearance of the lesion. Postoperative (C and D) T1 gadolinium-enhanced images demonstrate complete resection. T1 gadolinium-enhanced axial (E) images showing 4 lesions after 2 gamma knife radiosurgery procedure.

Table 1
Sequential management of different brain lesions.

Lesions	First radiosurgery 22-23 Gy		Second radiosurgery 22-23 Gy		Surgery	
	Pre-MRI (size in mm)	Post-MRI at 4 months (size in mm)	Pre-MRI (size in mm)	Post-MRI at 2 months (size in mm)	Pre-op MRI (size in mm)	Post-op MRI
Left frontal cortical	18	15	15	19	21	Complete excision
Left insular	9	7	7	7		
Right parafalcine	–	13	13	15		
Left external temporal	–	13	13	17		
left temporal cortical	–	–	–	5		

Pre-MRI: preprocedural; Post-MRI: postprocedural; Pre-op: preoperative; Post-op: postoperative; MRI: magnetic resonance imaging.

Following the 2 radiosurgical treatments, the patient presented a neurological deterioration with increased headache, nausea, and right hemiplegia that may have been related to the increase in left frontal lesion and peri-lesional edema. The left frontal lesion was progressive despite the two gamma knife procedures. In August 2017, using an operating microscope, a macroscopically complete excision of this voluminous left frontal lesion was performed. The patient was placed in a supine position, with her head turned 20° to the right, fixed in a Mayfield caliper slightly anteflected. A left frontal cranial flap was formed centered on this frontal lesion. A transfrontal corticotomy was performed with bipolar coagulation preserving the white matter tracts. Using an operating microscope, this voluminous left frontal lesion was reached without any difficulty. This lesion was hemorrhagic, indurated, the vascularization

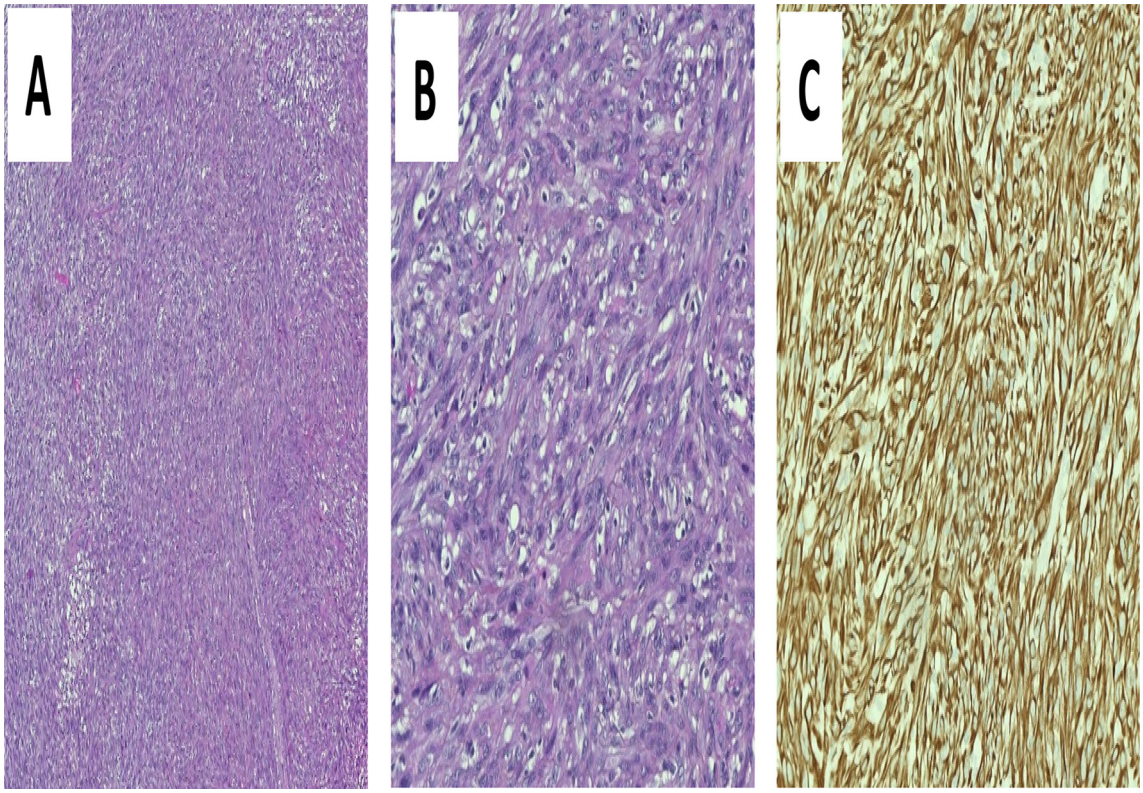

Fig. 2. Left frontal metastatic thymic carcinoma. A. Histological study shows the presence of a malignant tumor proliferation constituted by cells arranged in the form of sheets or bundles (HPS × 5). B. High magnification cells are pleomorphic, with eosinophilic cytoplasm (HPS × 20). C. Complementary immunohistochemical techniques performed showed a diffuse and intense expression of pankeratin AE1/AE3 (AE1/AE3 × 20). HPS: hematoxylin, phloxine, saffron.

of which originated from the subpial artery and two meningeal branches. Resection continued in a fragmentary manner until complete resection. Control was performed under the operating microscope of the tumor bed at the end of the procedure.

Immunohistochemical examination of operative specimens was compatible with a metastatic sarcomatoid thymic carcinoma (Fig. 2).

Postoperatively, the patient experienced an improvement in her neurological symptoms. The November 2017 brain magnetic resonance imaging revealed a macroscopically complete resection of the left frontal lesion without residual tumor (Fig. 1C–D). Four months after the surgery, the patient had a rapid secondary progression of the disease mainly at the cerebral, hepatic and bone level. The patient died 14 months after the initial diagnosis.

3. Discussion

We report a rare case of metastatic sarcomatoid thymic carcinoma in the brain. TETs are divided into thymomas and thymic carcinomas, depending on the preservation of the histological features of the thymic gland. The classification system of the World Health Organization, established (WHO) in 2004, divides thymomas into groups A, AB and B1-3 according to cell morphology and degree of atypia (Table 2) [4]. TETs occur mainly in the 40 to 60 age group and also affect both men and women [5].

The Masaoka classification system [6] is used to define the extent of the disease, which is strongly correlated with the prognosis (Table 3). Thymic carcinomas are more likely to metastasize than thymomas, with the pleura being the most common metastatic site, followed by bone and liver [7]. The 5-year survival rate for stage IV TETs of all histology is 50%, [8] with thymic carcinoma, the rates being 40% for stage IVa and 30% for stage IVb [9].

Table 2
World Health Organization Thymoma Grading System.

Type	Description
Type A	Predominantly comprised of cells with elongated or spindle-shaped nuclei
Type AB	Comprised of type A and type B cells
Type B	Predominately comprised of cells that have a dendritic or plump appearance, with B1, B2, and B3 subtypes designated by progressive degrees of atypia
Thymic carcinoma	Marked cellular atypia, nuclear pleomorphism, and mitotic activity consistent with maligna

Table 3
Masaoka Staging System for Thymic Tumors.

Stage	Description
Stage I	Tumor encapsulated in the thymus that may invade into but not through the capsule
Stage II	Tumor invades beyond the capsule into nearby fatty tissue; does not break through the pleura or pericardium
Stage III	Tumor extends into neighboring tissues or organs, including pericardium, lungs, and main blood vessels
Stage IVa	Tumor spreads widely throughout the pleura and/or pericardium
Stage IVb	Extrathoracic spread

The prognosis in thymic carcinoma is related to the extent of surgical excision of the primary tumor and histological grade. Despite aggressive local treatment, patients with thymic carcinoma tend to experience a tumor relapse to distant sites, including regional lymph nodes, bones, liver and lungs. Brain metastases due to thymic carcinoma are rarely reported and there is an increased risk of secondary disease in patients with thymus tumors [2,3].

Table 4
Review of thymic epithelial tumor metastases to the central nervous system, 1890 to present.

Authors [references]	Number	Age (years)	Sex	Symptoms	Tumor Location	Treatment	Histology	Outcome
Meigs, 1894 [11][a]	1	21	M	Cranial neuropathy	Cranial	–	Thymoma	–
Symmers, 1921 [11][a]	1	56	M	–	Dural-based	–	Thymoma	–
Danisch, 1928 [11][a]	1	3.5	M	–	Spinal meninges, nerve root, choroid plexus	–	Thymoma	–
Lowenhaupt, 1948 [11][a]	1	27	F	–	Cortex, spine	Surgery	Thymoma	–
Mottet, 1964 [12]	1	32	M	Diplopia, dysarthria, headache	light hemisphere with leptomeningeal attachment	None	Thymoma	Death 6 weeks after admission
Rachmaninoff and Fentress 1964 [13]	1	43	F	Papilledema and Babinski sign	Left temporoparietal lobe	Surgery and radiation	Thymoma	Symptom improvement, recurrence 2 years later
Butterworth et al., 1973 [14]	1	36	M	Paresthesias in neck, arms, and chest; cranial neuropathies	Meninges, nerve roots, pituitary gland	No treatment	Thymoma	Death 15 days after diagnosis
Macdonald et al., 1978 [15]	1	14	F	Headache	Occipital dural-based tumor	Surgery and radiation	Thymoma	No symptoms 9 months postoperative
Jose et al., 1980 [16]	1	49	F	–	Left hemisphere	Radiation and chemotherapy	Thymoma	Death 7 months after diagnosis
Wick et al., 1981 [17]	1	25	F	Lethargy, nausea, cranial neuropathies	Cranial nerves, choroid plexus, medulla, midbrain,	No treatment	Thymoma	Death 3 days after hospital admission
Suzuki et al., 1981 [18]	1	56	F	Gerstmann syndrome	Left parietal lobe and right centrum semioval	Surgery and radiation	Thymoma	Symptoms improved postoperatively
Yoshida et al., 1981 [19]	1	49	F	Intracranial hypertension	Multiple intracranial lesions	No treatment	Thymoma	Death 3 months after diagnosis
Ichino et al., 1983 [20]	1	46	F	–	Occipital lobe	Chemotherapy	Thymoma	Death from pneumonia
Arriagada et al., 1984 [21]	5	–	–	–	–	Treatment of primary tumor	Thymic carcinoma	–
Fornasiero et al., 1984 [22]	1	54	M	–	–	Radiation and chemotherapy	Thymoma	–
Maeda et al., 1984 [11]	1	61	M	–	Bilateral cerebral and cerebellar hemispheres, vermis	Partial surgical resection	Thymoma	Death 7 weeks after diagnosis
Dewes et al., 1987 [23]	1	49	M	Left hemiparesis	Right parietal	Surgery and radiotherapy	Thymic carcinoma	Alive 2 years postoperative
Mizushima et al., 1988 [24]	1	56	M	Gerstmann syndrome, right hemiparesis	Left temporoparietal	Needle aspiration followed by resection	Thymoma	Death within 1.5 years
Yamamura et al., 1993 [25]	1	72	M	Left hemiparesis	Parafalcine	Surgical resection	Thymic carcinoma	Improvement in symptoms
Nicolato et al., 2001 [26]	1	55	M	Left hemianopsia	Left temporal and right occipital lobe	Evacuation of cystic right occipital lesion with stereotactic radiosurgery for both nodules	Thymic carcinoma	Alive 3 years postoperative
Ahn et al., 2002 [27]	1	31	F	Headaches, left limb weakness	Right temporal dural-based mass	Surgical resection and radiation	Thymic carcinoma	No recurrence at 12 months postoperative
Chalabreysse et al., 2002 [2]	4	–	–	–	–	–	Thymic carcinoma	–
Al-Barbarawi et al., 2004 [28]	1	49	M	Headache, hemiparesis dysphasia	Left frontal and left parietal lobe lesions	Craniotomy for left frontal lobe lesion	Thymic carcinoma	Death 20 days postoperative with new cerebellar lesion and expansion of parietal lesion
Tamura et al., 2004 [29]	1	50	M	Headache and scalp mass	Right occipital bone with extension to intradural and extracranial spaces	Surgical resection and chemotherapy	Thymic carcinoma	Doing well 6 months postoperative
Kanayama et al., 2005 [30]	1	80	M	Right ptosis, right visual loss, and left hemianopsia, endocrinopathies	Sellar/suprasellar mass	Surgical resection	Thymoma	Death 6 months postoperative because of multiple metastases

Table 4 (*Continued*)

Authors [references]	Number	Age (years)	Sex	Symptoms	Tumor Location	Treatment	Histology	Outcome
Kong et al., 2005 [31]	6	Avg 48 yrs	4 M 2 F	Headache only in 4 patients; headache and hemiparesis in 1; hemiparesis in 1 patient	Cerebral hemispheres, 1 cerebellar lesion, 1 brainstem lesion	2 with surgery and WBRT; 1 with surgery, WBRT, and radiosurgery; 2 with WBRT only; 1 conservative treatment only	Thymic carcinoma	3 deceased at 2, 7, and 9 months postdiagnosis; 3 alive at 2, 2, and 9 months s/p diagnosis
Ersahin et al., 2007 [32]	1	38	M	Dysphasia, disequilibrium, memory loss	> 70 cystic lesions	No treatment	Thymic carcinoma	Death on hospital day 2
Gamboa et al., 2008 [33]	1	77	F	Seizures	Multiple cerebral and cerebellar lesions	Surgical resection of 1 lesion	Thymoma	Death at 16 months
Walid et al., 2008 [34]	1	49	F	Headache, SIADH	Right temporal mass	Surgery	Thymic carcinoma	–
Tsutsumi et al., 2010 [35]	1	39	M	Ophthalmoplegia and visual field deficit	Extra-axial left middle cranial fossa	Surgery and chemotherapy	Thymic carcinoma	Death at 16 months
Yang et al., 2010 [36]	1	42	M	Headache, vomiting	Multiple intracranial metastases	Surgery, chemotherapy, radiation	Thymic carcinoma	–
McLaughlin et al., 2011 [37]	1	22	F	Headaches	Left frontal and right parietal lobe	Surgery and radiosurgery	Thymoma	Alive without recurrence at 32 months
Kosty et al., 2016 [38]	1	47	M	Headaches, nausea, and ataxia	Left cerebellar mass	Surgical resection	Thymic carcinoma	One year after surgery, no evidence of recurrence
Present case	1	73	M	Headaches, nausea and right hemiplegic	Multiple intracranial metastases	2 radiosurgery and surgery	Thymic carcinoma	Death 14 months after diagnosis

M: male; F: female; WBRT: whole brain radiation therapy; SIADH: syndrome of inappropriate antidiuretic hormone secretion.
[a] Cited in Maeda et al. [11].

Surgery is the mainstay of treatment of stage I and II tumors. Patients with stage III and IV tumors are usually treated with platinum-based chemotherapy and surgery, if possible [10].

Radiotherapy is generally used in cases of incomplete resection, high grade histology (WHO types B2, B3) and thymic carcinomas (WHO type C) and where the tumor invades the surrounding structures. In cases of unresectable stage III and IVa tumors, treatment modalities include chemotherapy, radiotherapy and sometimes surgery, particularly if neo-adjuvant chemotherapy does not result in resection of the lesion [10].

The response of cerebral metastases of thymic carcinomas to stereotactic radiosurgery gamma knife has not yet been conclusively demonstrated. In the three cases [26,31,37] reported, gamma knife radiosurgery treatment had been used to control brain disease. In our case, radiosurgery was not able to control her brain disease and she eventually succumbed to the rapid secondary progression of the disease mainly to the cerebral level. A case series analysis, on the factors of failure or success of radiosurgery in brain metastases of thymic carcinoma would be interesting.

We reviewed the literature in English from 1890 to today and found 45 cases of metastatic TET in the brain. The epidemiological, diagnostic, therapeutic and monitoring characteristics are summarized in Table 4. For Kosty et al. [38], a significant interpretation of these data is strongly limited by patient selection, reporting bias, and variable follow-up periods. However, surgery in the case of TET brain metastases probably does not have a negative impact on the results.

4. Conclusion

Thymic carcinoma is a rare and aggressive neoplasm. Although these metastases are associated with a poor overall prognosis, a survival of more than one year can be achieved with surgical resection and multimodal treatment of the primary tumor. The treatment of secondary cerebral disease depends on the clinical condition of the patient; however, an improvement in survival can be observed after resection of the intracranial tumor either by surgery or stereotactic radiosurgery.

Disclosure of interest

The authors declare that they have no competing interest.

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