

*Case Report*

Supratentorial Embryonal Tumors in the Elderly: Diagnostic Pitfalls and Clinical Prognosis

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Supratentorial embryonal tumors are very rare malignant tumors of neuroectodermal origin, characterized by an aggressive clinical behavior. They occur prevalently in children. They have been sporadically described in adults and represent an even rarer occurrence in elderly patients, raising many issues on the diagnostic pitfalls and their appropriate management. We present an unusual case of embryonal tumor in a 62-year-old man who presented with speech disorder, and partial deficit of the left 3rd and 5th cranial nerves secondary to a left temporo-insular embryonal tumor: the clinico-radiological features, histopathological insights, therapeutic options and results are discussed along with a review of the most relevant literature, addressing the specific issue of differential diagnosis and the expected results in the elderly population.

KEYWORDS: Elderly, Embryonal tumor, Prognosis, Supratentorial**■ INTRODUCTION**

The embryonal tumors other than medulloblastoma represent a heterogeneous group of malignancies characterized by poorly differentiated neuroepithelial cells and generally aggressive behavior, localized in the supratentorial compartment. They have been historically indicated as supratentorial primitive neuroectodermal tumor (sPNET) (6). These tumors occur prevalently in children, representing about 2.8% of all primary brain tumors of childhood and adolescence. They represent an extremely rare occurrence in elderly patients aged 60 years or older, raising many issues on the diagnostic pitfalls and management strategy (1,3,4,5,7,10,12,13,15).

We report the case of a 62-year-old man affected by a temporo-insular embryonal tumor with a review of the most relevant literature, addressing the specific issue of differential diagnosis and the expected results in the elderly population.

■ CASE REPORT

A 62-year-old male patient presented to our Department with a two-month history of short-term memory impairment, associated with aphasia nominum, semantic paraphasias, numbness sensation of the left hemi-face and partial left third cranial nerve deficit.

Magnetic resonance imaging (MRI) of the brain showed the presence of a left temporo-insular lesion (Figure 1A-F). The patient underwent subtotal removal through a left fronto-temporal craniotomy. The lesion was classified as sPNET, World Health Organization (WHO) grade IV (Figure 2A-F).

The postoperative course was characterized by a slight improvement of the preoperative symptoms. He underwent chemotherapy and radiotherapy. A 6 month-postoperative MRI documented tumoral re-growth, for which a reoperation was proposed. However, the patient refused. In the next four months, he experienced a progressive sensory deterioration, until a state of coma and subsequent death.

■ DISCUSSION

The term supratentorial PNET was originally used to describe central nervous system (CNS) tumors that histologically resembled medulloblastoma, but originated outside the cerebellum (9,12). The recent WHO classification of CNS tumors, published in 2016 (6), introduced major changes regarding these tumors' definition, starting with the removal of the term PNET. Much of the re-classification was driven by the recognition that many of these rare tumors display amplification of the C19MC region on chromosome 19 (19q13.42). Therefore, it includes embryonal tumors with abundant neuropil and true

rosettes (ETANTR), ependymoblastoma and medulloepithelioma. Recent studies have shown that adult sPNET cases present some significant differences: high incidence of TP53 mutations, no amplification of the c-myc/N-myc genes, and presence of IDH1 mutations (2).

The incidence of cases reported in the adult population is extremely low, accounting for less than 0.5%; they occur prevalently in the third decade of life, resembling the presence of two peaks in the age profile for sPNET onset: childhood and middle age (5,15). During the last decade, the interest on adult patients affected by sPNET has increased progressively due

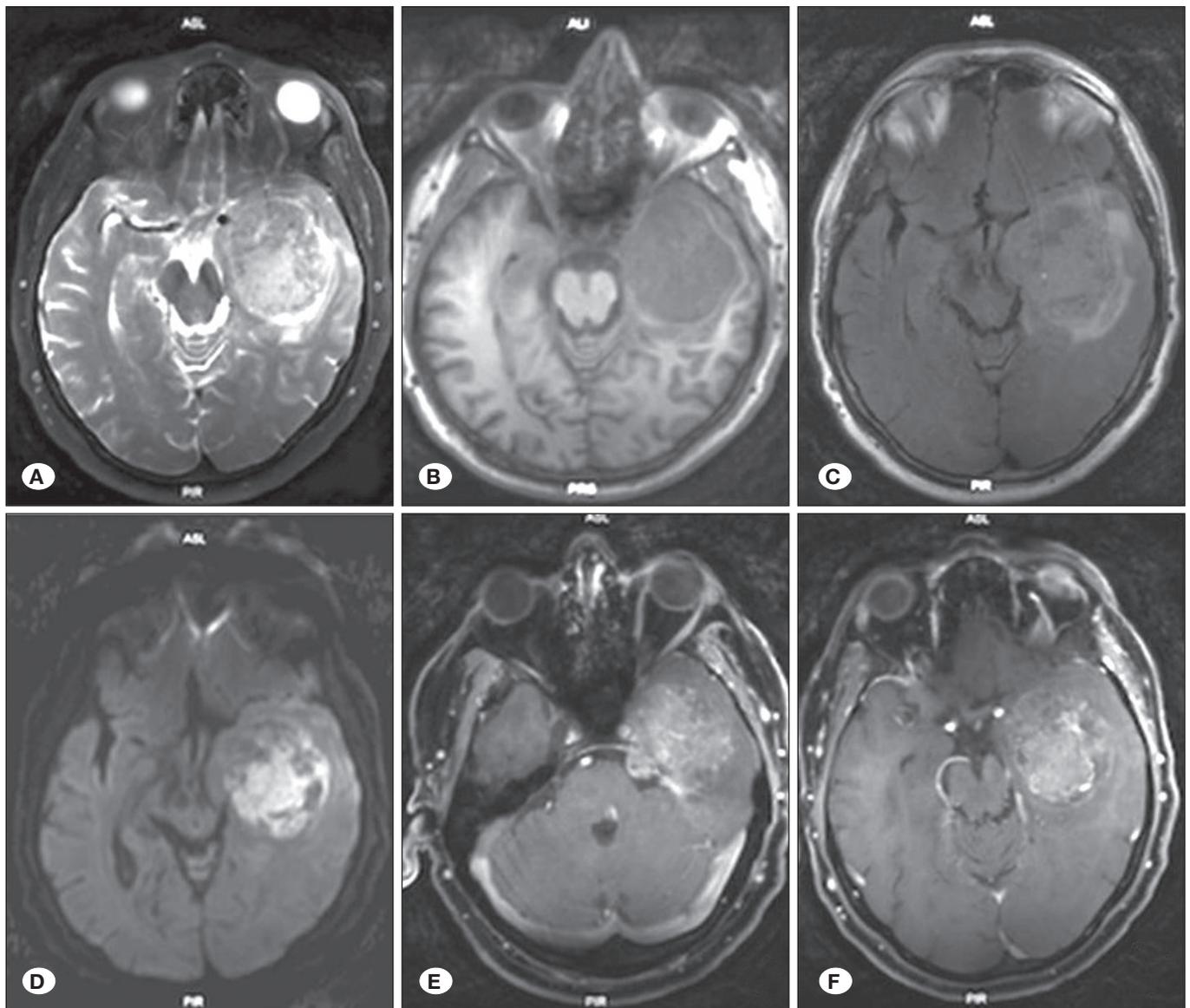


Figure 1: MRI showing a huge well circumscribed, oval shaped, left temporo-insular lesion (about 5 cm diameter), associated with perilesional edema; an extraaxial origin from the anterior edge of the left tentorium with a small infratentorial component invading the homolateral pre-pontine cistern was depicted. **A-C)** T2- and **B)** T1-weighted axial images. The tumor appeared isointense to cortex lesion on **A)** T2-weighted and **C)** T2 – FLAIR MRI images, and restricted in **D)** diffusion sequences (DWI). **E-F)** On T1-weighted axial images with gadolinium there was inhomogeneous contrast enhancement with peripheral colligative areas, involving the entire left Meckel cave, deforming the third and the left lateral ventricle and displacing the ipsilateral middle cerebral artery (MCA). These findings were highly suspicious for a lesion of extra-axial origin, like a meningioma.

to the better identification of these tumors (5,15). According to the literature review, there are only 20 cases of patients aged 60 years or older reported so far, who deserve a particular discussion (Table I).

Patients ranged in age from 60 to 88 years (mean 68.6 years) with a male predominance (ratio 2.5:1). In these cases, most of the lesions were located in the temporal and parietal lobes, compared with a prevalent localization in the frontal lobe in adult patients (15); one patient had a corpus callosum seeding, whereas bilateral ventricles lesions were observed in another one. None of them had a pineal localization, as reported in the general adult series (15).

The most common presenting symptoms were focal neurological deficits and intracranial hypertension-related symptoms; seizures, frequently occurring in children, were not reported.

On neuroradiological examination, sPNETs appeared as large masses, rarely associated with necrosis cysts, calcification and hemorrhage (11). They displayed heterogeneous signal intensity, with the solid portion of the tumor typically showing hypointensity on T1-weighted images and hyperintensity on T2-weighted images; intense homogenous enhancement was often described on contrasted T1-weighted sequences. Peritumoral edema was also depicted (5,11). On the basis of these findings, the rarity of this tumor in the elderly may raise some difficulties in the differential diagnosis. sPNET in adults usually looks like a high-grade astrocytoma or anaplastic oligodendroglioma on computed tomography and MRI; however tumor cyst, calcification and lobulating contour with good demarcation may be more frequently observed

in sPNET than in high-grade gliomas. It may appear more similar to a meningioma as in our case. This hypothesis is sustained by epidemiological data (meningiomas are common intracranial neoplasms with a maximum incidence between the fifth and sixth decade), presence of degenerative necrotic - cyst/pseudocyst, perilesional edema (depicted in 60% of meningiomas) and intense and homogeneous contrast enhancement with a “dural tail” sign associated (5,8,14).

The initial staging should include spinal MRI and cerebrospinal fluid (CSF) cytology, in order to plan cranio-spinal radiotherapy or intrathecal chemotherapy, as generally applied in children. Indeed, CSF spreading is one of the few prognostic factors correlated with outcome in adult sPNET (15).

Age was the other factor associated with worse survival. According to Zheng et al.(15), the 1 year survival rate is better for patients aged <60 years (83.3% versus 40%), although not statistically significant.

Generally speaking, sPNET in adults are rarer and usually have a worse prognosis compared to their infratentorial counterpart (medulloblastomas), as well as compared with sPNET in the pediatric population. More than 2/3 of the entire series of elderly patients died after a mean follow-up of 10.9 months (range 2-62 months) (5,13,15). Due to the small number of cases analysed, we are not able to draw conclusions, especially with regard to those patients who had a better clinical follow-up; however, data emerging from the literature depicted age at onset, surgical resection, extent of resection and radiotherapy as good prognostic factors (15). Zheng et al. observed that radiotherapy and both chemotherapy and

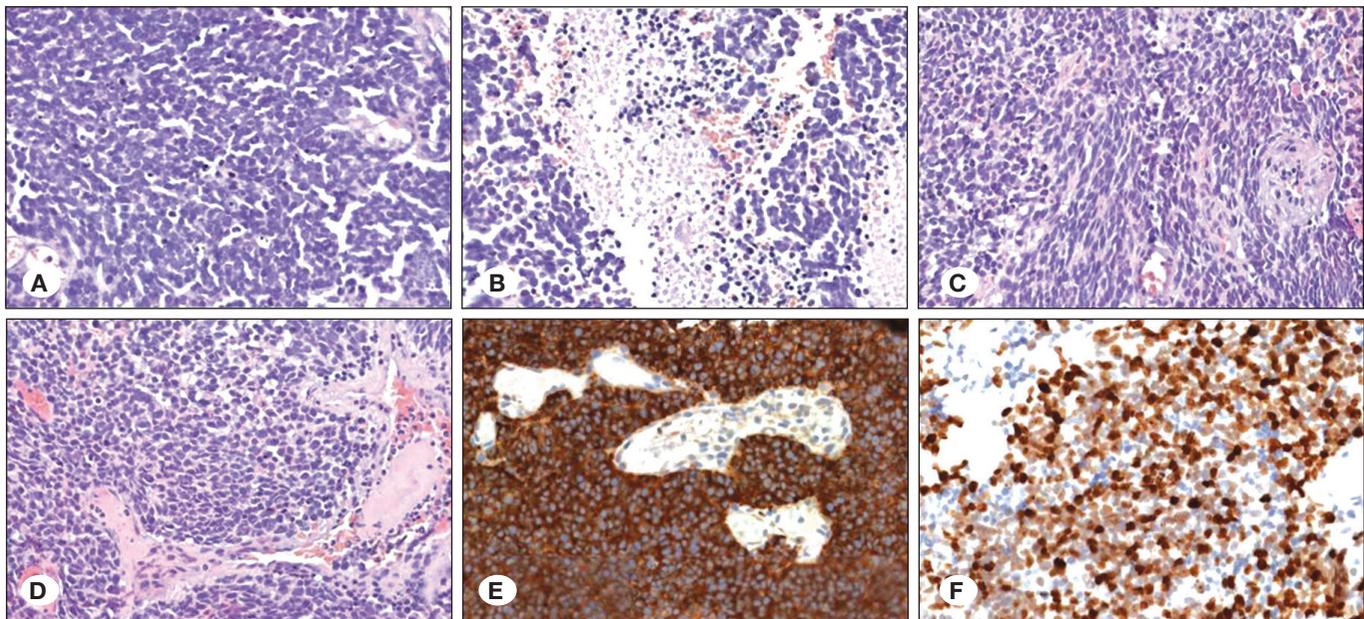


Figure 2: **A)** Hematoxylin & Eosin (H&E) stain (400x): small cell monomorphic proliferation with addensed chromatin, little cytoplasm, with some thickening of the blood vessel wall, **B)** H&E stain (400x): presence of oat-cells (short, bluntly spindle-shaped, anaplastic cell), conforming to PNETs, **C)** H&E stain (200x): vital cell populations with pathways of coagulative necrosis, **D)** H&E stain (400x): presence of mitotic cells and apoptotic bodies (dense and small nucleus). This feature represents the high grade malignancy, **E)** (400x): Immunohistochemistry of synaptophysin, bright diffuse staining throughout the entire cytoplasm of all cells, **F)** (400x): Ki67 antigen immunostaining (MIB 1 monoclonal antibody): mark in proliferating cells (G1-S e M phases), nuclear positivity >85-90%

Table 1: Summary of the Elderly sPNET Cases Reported in the Literature

| Authors | Sex, Age (years) | Clinical onset | Radiological features | Surgical procedure | Adjuvant Therapy | Clinical follow-up | Radiological FU |
|-------------------------------|------------------|---|---|-------------------------------|--|--|---|
| 1 Grant et al. 1988, (3) | F, 66 | Progressive hemiparesis | L P lesion | Biopsy and subtotal resection | none | Died after 7 months | Not reported |
| 2 Ho et al. 1996, (4) | F, 65 | Not reported | R T lesion | Subtotal resection | No RT | Died after 8 months | Not reported |
| | F, 60 | Not reported | R P lesion | Subtotal resection | RT | Died after 4 months | Not reported |
| 3 Selassie et al. 1996, (10) | M, 77 | Not reported | L T lesion | Total resection | RT | Died after 6 months | Not reported |
| | M, 60 | Visual difficulty | Well circumscribed L O lesion | Subtotal resection | WBRT and CT (BCNU)-then Etoposide and cis-platinum | Died after 8 months | Metastatic lesions along the walls of lateral ventricles |
| 4 Takeuchi et al. 1998, (13) | M, 69 | 1 month history of Headache, memory deficit, aphasia. | Intra-axial L PO lesion | Subtotal resection | WBRT and focal boost; CT (carboplatin) | Alive at 30 months | No recurrence |
| | F, 62 | 2 months history | Well circumscribed Temporal lesion (5 cm in diameter) | Subtotal resection | RT | Alive 18 months KPS 70 | No recurrence |
| 5 Majos et al. 2002, (7) | 67 | Not reported | Fr lesion (7.5 cm) | Partial resection | Not reported | Not reported | Not reported |
| 7 Balafouta et al. 2003, (1) | M, 60 | 2-month history of headache, aphasia, right hemiparesis | Well circumscribed FrP lesion | Biopsy | WBRT and focal RT; Neuraxis RT and CT (CCNU) | Clinical deterioration after 10 month. Died after 12 months from diagnosis | Regrowth By the 10 month-control |
| | F, 88 | Disturbance of consciousness; left hemiplegia | Well circumscribed R FrT lesion | Biopsy | CT (MCNU) | Died after 5 months | Initially reduction; growth by 6 weeks after 2nd cycle CT |
| 8 Shingu T. et al. 2005, (12) | F, 63 | Not specified | R P lesion 3.5 cm; multiple lesions | Biopsy | CT (Cisplatin, Etoposide); Brain RT | Died after 6 months | Not specified |
| | M, 75 | Not specified | R T lesion 4 cm and CSF spreading | Gross total removal | none | Died after 8 months | Not specified |
| 9 Zheng YC et al. 2014, (15) | M, 76 | Not specified | R Fr lesion 2.5 cm and CSF spreading | Gross total removal | Brain RT | Died after 2 months | Not specified |
| | M, 81 | Not specified | Corpus Callosum 1 cm; multiple lesions | Biopsy | Brain RT | Died after 18 months | Not specified |
| M, 77 | Not specified | Left temporal lesion 4.5 cm | Biopsy | CT (Temozolamide); RT | Died after 62 months | Not specified | |
| | M, 61 | Not specified | Bilateral ventricle lesion 3 cm and CSF spreading | Partial resection | none | Died after 2 months | Not specified |

Table 1: Cont.

| Authors | Sex, Age (years) | Clinical onset | Radiological features | Surgical procedure | Adjuvant Therapy | Clinical follow-up | Radiological FU |
|-----------------|------------------|--|--|--------------------|------------------|-----------------------|-----------------------------------|
| | F, 62 | Not specified | Bilateral temporal multiple lesions (2.5 cm) and CSF spreading | Partial resection | RT | Died after 7 months | Not specified |
| | F, 66 | Not specified | L T 1.5 cm and CSF spreading | Partial resection | RT | Died after 10 months | Not specified |
| | M, 75 | Not specified | L T 4 cm | Subtotal resection | none | Alive after 39 months | Not specified |
| | M, 70 | Not specified | R T lesion 2.8 cm | Biopsy | RT | Alive after 37 months | Not specified |
| 10 Present case | M, 62 | Memory deficit, aphasia, left III c.n. deficit | L T-insular (5 cm) | Subtotal resection | RT and CT | Died after 10 months | Re-growth by the 6 month- control |

CSF: cerebrospinal fluid; **CT:** chemotherapy; **F:** female; **M:** male; **Fr:** frontal; **L:** left; **O:** occipital; **P:** parietal; **R:** right; **RT:** radiotherapy; **T:** temporal; **WBRT:** Whole brain radiotherapy; **KPS:** Karnofsky Performance Score; **CCNU:** Lomustine; **BCNU:** Carmustine

radiotherapy were marginally significant for better survival, whereas chemotherapy alone did not improve survival at all (15). However, due to a relative radioresistance of these tumors compared to medulloblastoma, the addition of multi-regimen chemotherapy is considered of therapeutic value.

■ CONCLUSION

There is a general agreement to consider complete removal of the tumor when feasible; followed by adjuvant radiotherapy and chemotherapy, even in elderly patients should the general conditions allow the entire treatment.

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