

A very rare, petro-clival, neurothekeoma tumor. Case Report

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Abstract: Known as nerve sheath myxoma too, neurothekeoma are benign tumors, usually arise in the skin of the head, neck region and upper extremities, in young females. Cerebral neurothekeoma are very rare, a few cases were already described in the parasellar area, in the middle cranial and posterior fossa. We present a petro-clival neurothekeoma. A 78-year-old male was admitted for two years left fronto-temporal headache completed in the last 6 months with left trigeminal V1 neuralgia, left facial hypoesthesia, diplopia, swallowing disorders for liquid foods, balance disorders. From his medical records we noticed: stage 2 chronic kidney disease, hypertension, prostate adenoma, dyslipidemia hypercholesterolemia. The MRI showed a macronodular petro-clival mass in hiper T2, hipo T1, flair iso signal; normal cerebral angiography. The patient was operated on using a left retrosigmoid, retromastoidian approach. A 4/3/3 cm tumor, gray, encapsulated, soft consistency, partially cystic, less bleeding, attached to the dura, displacing the basilar artery and brain stem controlateral, encasing the trigeminal nerve. The tumor was totally removed with a good postop evolution. Six months follow up he had no more facial pain, but only persistant left facial hypoesthesia. Histologically the tumor had lobular appearance with spindle or stellate cells embedded in abundant myxoid background. The tumor cells were diffusely positive for S100, PGP9.5, CD 34 positive in vessels, Ki67 positive in 5%. Cranial MRI performed one month after surgery did not show any residual tumor. Also known as nerve sheath myxomas, neurothekeoma are rare benign tumors. For intracranial neurothekeoma surgical indication is mandatory

Key words: intracranial neurothekeoma, petro-clival tumor, nerve sheath myxoma.

Introduction

Neurothekeoma is a benign, predominantly cutaneous tumor, of probable nerve sheath origin (1-7), quite common, presented as a solitary nodule in the head (5), oral cavity (7), hypopharynx (8), tongue (9), maxilla (10), breast (11), neck shoulders or upper limbs (12), peripheral nerve - median nerve (13), spinal intradural (6)(14)(15), even cervical - intramedullary (14). The intracranial localization was reported in only few cases

(16)(17): disposed in the pituitary area (18), medium (19) and posterior fossa (20)(21): cerebellopontine angle (22), pons (23). After our knowledge the current report is first in world literature with neurothekeoma located petro-clival.

Case Report

A 78-year-old male was admitted in our clinic for two years left fronto-temporal headache completed in the last 6 months with

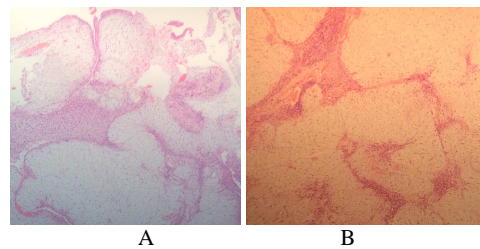
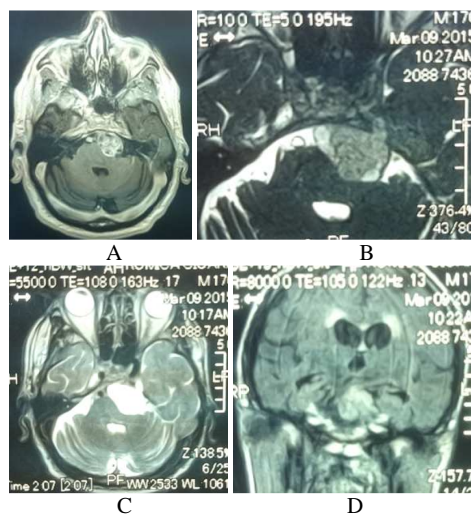
left trigeminal V1 neuralgia (cvasi constant, without benefit from analgesics), left facial hypoesthesia, diplopia, swallowing disorders for liquid foods, balance disorders. From his medical records we noticed: stage 2 chronic kidney disease, hypertension, prostate adenoma, dyslipidemia, hypercholesterolemia. Biochemical investigations showed too: a slight nitrate retention: urea 74 mg/dl, creatinina 1.7 mg/dl and slight hypopotasemia 3,4 mmol/l.

Axial, coronal, and sagittal MRIs of the head displayed: an extranevraxial petro-clival mass, well delineated, with heterogeneous tissue component with peripheral cystic component, hypointense on T1-weighted images, hyperintense on T2-weighted images with heterogeneous enhancement following contrast agent administration, measuring 33 mm transverse Ø, 23 mm antero-posterior Ø and 37 mm cranio – caudal Ø, with distortion of the brain stem, left nerves VII, VI, III; also the adjacent arteries: basilar trunk, superior left cerebellar artery and posterior cerebral artery (Figure 1). Important periventricular demyelinating lesions and cerebral atrophy associated, dilatation of ventricular system with periventricular lucency.

Figure 1 - Preoperative MRI: A-C axial, D coronal images showing the extranevraxial petro-clival tumor mass, with heterogeneous tissue component and peripheral cystic component, distorting the brain stem, left nerves VII, VI, III, the adjacent arteries: basilar trunk, superior left cerebellar artery and posterior cerebral artery

Using a left retromastoidian, retrosigmoidian approach an encapsulated, gray tumor was discovered in the petro-clival area. This tumor has soft consistency, partially cystic, mixed with areas of fibrotic tissue, less bleeding, attached to the dura, encasing trigeminal nerve, displacing the basilar artery and brain stem contralateral. The tumor was totally removed. Postoperative evolution was uneventfull; six months follow up he had no more facial pain, but only persistant left facial hypoesthesia.

Histological and immunohistochemical staining was performed. Histologically the tumor was encapsulated by a thin fibrous connective tissue and composed by fusiform and stellate cells, with loose, pale, myxoid stroma; arranged in ovoid lobules of varying sizes separated by fibrous septae; rare high cell density areas presenting cells with central monomorphic nuclei showing spindle-shaped extensions and clear peripheral cytoplasm were observed. No mitosis and mild nuclear pleomorphism was noted (Figure 2).



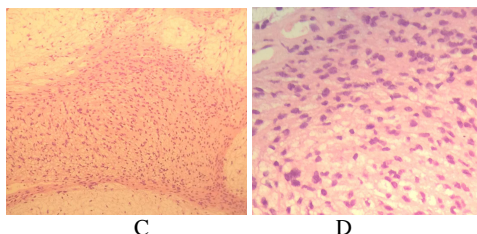


Figure 2 - A. col. H.E. 10 x 4 overview image: low density cells, arranged in lobules of varying sizes, separated from conjunctival vascular septa; fusiform and stellate monomorphic nuclei with schwannoid aspect
 B. col H.E. 10 x 10: tumor cells lobules arranged in a lax, pale, myxoid background, separated by conjunctival vascular septa with inflammatory elements
 C. col H.E. 10 x 20 : lax, mixoid, peripheric cellular tumoral areas and central tumoral area with Antoni B schwannoma type appearance
 D.col H.E. 10 x 40 detail: "schwanoid" tumoral area

On immunohistochemical studies diffuse positive staining of the cells with S-100 and vimentin was observed. Glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), cytokeratin antibody (MNF116) and neurokinin 1 (NK1) were negative. CD34 was positive in vessels and Ki67 was positive in 5% of cases. These histological and immunohistochemical findings are considered characteristic of neurothekeoma, with low relevant aggression proliferation (Figure 3)

After operation facial pain progressively diminished; balance disorder and swallowing disorders for liquid foods disappear. A 5 day postop MRI demonstrate important reduction of mass effect on brain stem, no parenchimal tumor mass anteriorly described (Figure 4) Six months follow up he had only persistent left facial hypoesthesia. No chemotherapy or radiation was used in this case.

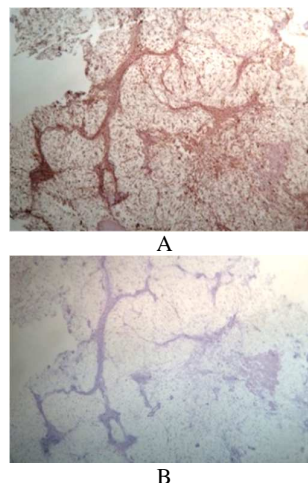


Figure 3 - Immunohistochemical stains:
 A. S100, 4 X 10: diffuse positivity in tumoral cells and negativity in vascular structures
 B. GFAP, 4 X 10: negative, proving no glial origin

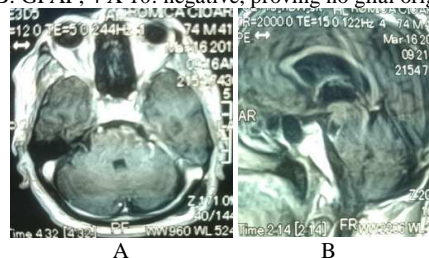


Figure 4 - Postoperative MRI: axial and sagittal T1 showing important reduction of mass effect on brain stem, without tumoral remnants

Discussion

Neurothekeoma is a benign, predominantly cutaneous neoplasm of presumed neural sheath origin, usually arising in the skin of the scalp, nose, orbital region especially eyelids, cheeks, paranasal sinuses, oral mucosa hypopharynx, chin, neck, the upper trunk, breast also in spinal topography of children and young adults as a flesh-colored solitary nodules solitary nodule with overlying erythema on cutaneous examination. The lesions range in size from about 0.5 cm to most commonly less than 2 cm in diameter; mean age of 25 years – but may occur at any age,

with a female preponderance, the male to female ratio is approximately 1:4,3 (1)(3)(17).

This tumor was initially described by Harkin and Reed (2) in 1969 by the name "nerve sheath myxoma". In 1980, Gallager and Helwig (3) termed the lesion neurothekeoma (greek: theke, sheath) to connote the histologic nested appearance in order to reflect the presumed origin of the lesion from nerve sheath; cells are usually spindle-shaped and arranged in fascicular or whorled patterns (5)(17). Epithelioid cells have been observed in these tumors. Several names were used for this tumor: "bizarre cutaneous neurofibroma", "plexiform myxoma", "myxoma of nerve sheath", "pacinian neurofibroma", cutaneous lobular neuromyxoma, perineurial myxoma reflecting the uncertainty regarding their true "histogenesis" or precise line of differentiation (15)(16)(22).

Histologically neurothekeoma on gross examination appear as dermal tumors commonly measuring 0.5 to 2 cm in dimension (2)(5). On microscopy (22)(24) neurothekomas could be:

- myxoid - generally agreed of neural origin, displaying a lobulated, non-encapsulated but well-circumscribed proliferation of stellate, spindle-shaped and epithelioid cells – less commonly situated in multiple, closely spaced nodules of varying sizes, with abundant eosinophilic, finely granular cytoplasm, embedded within a myxoid stroma. Due to the large amount of myxoid stroma separating the cells, the tumor cells are said to display a random growth pattern.

- cellular subtype: first described by Barnhill in 1990 (26), contains little myxoid material, hypercellular nests and fascicles of epithelioid cells with vesicular nuclei containing scant myxoid stroma, also sclerotic collagen, poorly circumscribed, no immunoreactivity to the S-100 protein (5). The nodules of cellular neurothekeoma are smaller than those of the myxoid subtype. Several

variants of cellular neurothekeoma are described: atypical or desmoplastic with low mitotic activity, with perineural and vascular invasion, osteoclastic giant cells in a minority of cases, neurothekeoma mimicking nevomelanocytic tumors (2)(3)(5)(17)(26) are described.

- intermediate subtype demonstrate a whorled growth pattern with features of both cellular and myxoid variants

The etiology of neurothekeoma arising in the parenchyma remains enigmatic (5)(25): by neural differentiation – see myxoid areas similar to classic myxoid neurothekeoma, by smooth muscle differentiation - myofibroblastic or by the epithelioid variant of dermatofibroma represented by cellular neurothekeoma. Since the time of their first description, it has been reported that the probable cell of origin could be the Schwann cell innervating the blood vessels (2)(3)(17)(22). Although they are similar in appearance and in behavior, neurothekeoma and nerve sheath myxoma are likely not of nerve sheath origin, as implied by the term and not related histogenetically. Another possible origins could be: perineural cell of the nerves in the dura mater, around the blood vessels or by extreme differentiation of the precursor pluripotent cell resting inside the brain parenchyma under suitable conditions to the schwannian phenotype (31).

Neurothekeoma immunohistochemistry (24)(27)(28) demonstrates:

- for myxoid subtype: diffuse S100 protein and glial fibrillary acidic protein (GFAP) immunoreactivity, supporting its schwannian differentiation. The myxomatous type generates large amounts of myxoid matrix and is typically immunoreactive to the S-100 protein (27).

- for cellular subtype: focal positivity for S100 protein in a minority cases (5), NK1/C3, an antibody that stains neuroectodermal tissue and PGP9.5, a broad marker for neuroectodermally derived tumors

demonstrates positivity; but these two markers are not specific; smooth muscle actin (SMA) & neuron-specific enolase (NSE) have shown positivity. A very high sensitivity has S100 A6 is a member of the S100 protein family, but with low specificity.

Neurothekeomas can also show immunoreactivity to vimentin.

The tumor in our case was encapsulated, composed by fusiform and stellate cells, with loose, pale, myxoid stroma; arranged in ovoid lobules of varying sizes separated by fibrous septae, no mitosis and mild nuclear pleomorphism was seen, rare high cell density areas presenting cells with central monomorphic nuclei showing spindle-shaped extensions and clear peripheral cytoplasm. The immunohistochemical findings in our case shows: diffuse positive staining of the cells with S-100 and vimentin and negative glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), cytokeratin antibody (MNF116) and neurokinin 1 (NK1). CD34 was positive in vessels and Ki67 was positive in 5% of cases. The histological and immunohistochemical findings are considered characteristic of neurothekeoma, with low relevant aggression proliferation (fig. 3).

A rare variant of this neoplasm constitute the atypical cellular neurothekeoma (29) seen occasionally, starting from cellular and intermediate subtype. For this variant, large tumor size (up to 6 cm), atypical histologic features: cellular atypia (rounded or ovoid nucleus with abundant cytoplasm), few individual cell necroses, high mitotic rate ranged from 8 to 12 per 10 high-powered fields, marked cytologic pleomorphism correlates with local invasion: deep penetration extending into skeletal muscle and/or adipose infiltration, diffusely infiltrative borders, vascular invasion, possible recurrence if surgical excision of these lesions was incomplete, without metastases.

There are few reports referring to neurothekeomas with an intracranial location (16)(30)(31): disposed in the pituitary area (17), middle cranial fossa (18) and posterior fossa (20)(21): cerebellopontine angle (22), pons (23). The most common type of intracranial neurothekeoma is myxoid; characterized by hypocellularity, with small spindle or stellate cells loosely arranged in abundant mucinous stroma. On immunohistochemical staining, the tumor cells are typically immunoreactive to the S-100 protein (1-3,8), nerve growth factor receptor (p75NGFR), collagen type IV, CD34, glial fibrillary acidic protein, and CD.

In our case, the neurothekeoma was hypointense in T1-weighted images and hyperintense in T2-weighted images using MRI, similar to the MRI findings of a previously published neurothekeoma cases, with heterogeneous enhancement following gadolinium administration, of the peripheral portions and nonhomogeneous uptake in the central areas, which corresponded histologically to the vascular capsule and the myxoid center (2)(16)

In general surgery are beneficial, gross total resection is recommended and appears to be the definitive therapy (16)(31), without causing neurologic deficit for the patient; incomplete excision of neurothekeomas may lead to recurrence and local invasion (5)(17). Even if the trigeminal nerve was encased in the tumor – see our case, the resection was easy, without causing neurologic deficit for the patient.

Because both myxoid and cellular types of neurothekeomas are benign; there are no reported cases of metastases and the lesion does not need postoperative radiotherapy (31) or adjuvant chemotherapy (21). Follow-up for surveillance is necessary to detect recurrence in case of incomplete intracerebral neurothekeomas excision (16)(22).

Differential diagnosis in neurothekeomas should be made with (16)(18)(20)(22)(31):

-epidermal inclusion cysts, intradermal Spitz nevi, smooth muscle tumors, fibrohistiocytic tumors lipomas, pilomatrixomas, dermatofibromas, melanomas – sometimes difficult to be distinguish histologically from cellular neurothekeoma (melanocytic tumor are S100 positive, while cellular neurothekeoma are S100 negative), carcinomas

-schwannomas - well-circumscribed, sometimes cystic and often heterogeneously enhancing mass on MRI, usually seen in the oculomotor and the ambient cistern (32). The myxoid type of neurothekeoma may resemble to schwannoma, but lacks Verocay bodies and the Antoni A, B arrangement seen in schwannoma.

-meningiomas - typically isointense, contrast-enhancing extraaxial tumor with “dural tail”, surrounding the dural perimeter of the mass on MRI,

-epidermoid - hyperintense lesion.

-gliomas, meningiomas, sarcomas showing myxoid degeneration also cardiac myxomas metastasizing to the brain and soft tissue myxomas penetrating the skull

-spinal myxoid neurofibroma (6)(14)

-perineuromas are rare tumours which appear myxomatous, but no lobulation is noted, composed exclusively of perineural cells (22)

Conclusion

Intracranial neurothekeoma is a a benign, rare tumor, similar to the cutaneous type, with a distinctive clinic and histopathologic entity, unlikely to recur if totally excised, even in a petro-clival topography.

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