CASE REPORT

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Intracranial immature teratoma with a primitive neuroectodermal malignant transformation – case report and review of the literature

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Abstract

Introduction: Central nervous system (CNS) germ cell tumors are very rare, accounting for 0.3–3% of primary intracranial neoplasms; of these, the teratomas are even more uncommon. The immature variant of teratomas, defined by the presence of incompletely differentiated components resembling fetal tissues is considered as having a low, almost borderline malignancy state. *Case presentation*: A 35-year-old male presented with a left fronto-basal tumor. At surgery, a grey white tumor, mostly solid, was excised. The histopathological examination revealed an infiltrating teratoma. The histological spectrum varied from epithelial and mesenchymal mature to immature tissues. These structures were intimately mixed with significant areas of primitive neuroepithelial tubules and/or primitive neuroectodermal tissues. The diagnosis was that of an immature intracranial teratoma, with high histological grade WHO (World Health Organization) (Norris grade III). After surgical resection, a rapid infratentorial contralateral subarachnoid extension followed. The second tumor was largely formed by primitive neuroectodermal tumor (PNET)-like structures and rare mature epithelial tissues, meaning a PNET-like overgrowth or "malignant transformation" of an immature teratoma. After specific oncological treatment, the patient had a favorable evolution with no signs of relapse (2016). *Conclusions*: The present case highlights the value of the Norris grading system (mostly used in grading ovarian immature teratomas) in a very rare case of intracerebral immature teratoma with rapid subarachnoid extension caused by an unexpected secondary "malignant transformation".

Keywords: teratoma, immature, neuroectodermal, intracranial, overgrowth.

Introduction

Central nervous system (CNS) germ cell tumors are very rare, accounting for 0.3–0.6% of all primary intracranial tumors in the West, to 2–3% in far-east Asia, were the incidence of CNS germ cell tumors appears to parallel the greater frequency of their testicular counterparts [1, 2]. These tumors preferentially affect the midline structures of the brain, around the third ventricle, especially the pineal gland and the suprasellar compartment, and rarely other sites. Only 6.2% of patients are older than 35 years, and just in exceptional cases have late adult onset [1]. A clear excess of cases involves males (73%), especially teratomas (89%) [1]. Intracranial pure teratomas are uncommon, the histologically immature variant and those with secondary "malignant transformation" being exceedingly rare [1].

Mature intracranial teratomas consist exclusively of mature, fully differentiated tissues and are potentially curable by gross total resection [1]. Immature intracranial teratomas consist of immature, embryonic or fetal tissues, exclusively, to small amounts, admixed with mature tissues. Hypercellular embryonic mesenchyme, primitive neuroectodermal elements, clefts lined by melanotic neuroepithelium are more frequently encountered, and represent histological clues for the diagnosis of immaturity [1–3]. The immature variant of teratomas appears to occupy an intermediate position in terms of biological potential (survival rates after combined chemotherapy and irradiation, local recurrence, cerebrospinal fluid dissemination or hematogenous spread) [1, 2], between mature teratomas and high risk germ cell tumors of the brain (yolk sac tumors, embryonal carcinomas, choriocarcinomas and mixed lesions). Intracranial teratomas with malignant transformation or with a secondary malignant component contain an additional malignant component of conventional somatic type [1, 2, 4], composed of a single type of atypical cell population, with nodular or infiltrative pattern, mostly of carcinoma, sarcoma, primitive neuro-

ectodermal tumors, nephroblastoma, melanoma or neuroendocrine tumor type [1, 2, 4].

This report presents a clinical and pathological description of a very rare intracranial immature teratoma with "malignant transformation", or more correctly, with an overgrowth of a primitive neuroectodermal tumor (PNET)-like component. The case was followed-up for six years; it was decided to be presented now, given the favorable evolution.

Case presentation

A 35-year-old male patient, without significant medical history, presented suddenly repetitive partial simple motor seizures in the inferior right leg, which was believed at that time to be caused by spasmophilia. One month later, the motor seizures were accompanied by a slight decrease in muscle strength at the same level. The patient also accused intense headache that has not succumbed to mild analgesics. These symptoms worsened progressively, adding dysosmia. Physical examination revealed no other neurological signs, the clinical diagnosis being intracranial hypertension with complex partial tonic-clonic seizures.

Magnetic resonance imaging (MRI) revealed a well-circumscribed tumor, around 4 cm diameter, without pathological contrast enhancement but with apparently necrotic regions (Figure 1a). It was located in the basal part of the left frontal lobe (F1 and F2 gyrus) and interhemispheric, with extension onto the right gyrus. The tumor presented perilesional edema with slight subfalcial herniation and mass effect on the corpus callosum and on the frontal parts of the hemispheric ventricles (Figure 1b). The brain stem and the cerebellum were normal.

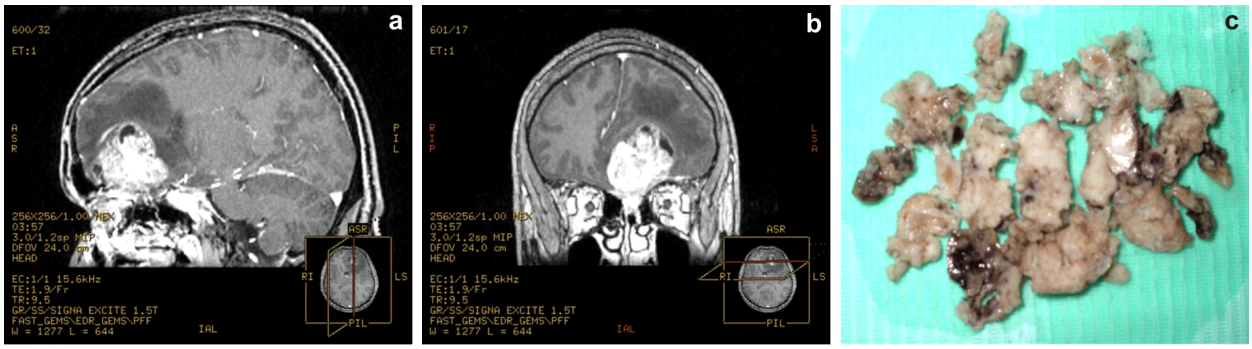

Figure 1 – ***(a) Sagittal section showing heterogeneous large frontal mass, with necrotic regions and perilesional edema; (b) Coronal section with perilesional edema, slight subfalcial herniation and mass effect on the corpus callosum and on the frontal parts of the hemispheric ventricles; (c) Tumor fragments, fleshy or white firm and with millimetric cysts.***

Subsequently, a craniotomy and gross total resection of the tumor was performed: the specimen was sent to the Laboratory of Pathology, clinically interpreted as left fronto-basal tumor of the olfactory groove. After one month, the patient presented a contralateral tumor relapse in the basal part of the right frontal lobe, apparently extraneuraxial (subarachnoid extension), as a 2.4/1.3 cm growth on the right sphenoid wing, extended onto the superior orbital fissure.

The first resection specimen consisted of multiple grey-white tumor fragments of 4.5/3/1.5 cm, 4.5/2/1.5 cm and 3.5/2/1.5 cm, containing also peritumoral tissue. The tumor was heterogeneous, with mostly soft, fleshy areas, firm white regions and multiple small millimetric cysts (Figure 1c).

After thorough microscopic examination of the whole tumor on Hematoxylin and Eosin (HE)-stained slides, a complex histology was revealed. A differentiation along ectodermal (Figure 1, a–d), endodermal (Figure 2, a, e and f) and mesodermal lines (Figure 2, a and e) was found, with disordered arrangement and containing mature and immature elements. Islands or sheets of well-differentiated keratinized squamous epithelium, glandular, tubular and acinar areas, few organoid, surrounded by bundles of smooth muscle, areas of fat, bone marrow and large sheets of dense small spindle cells were present. Immature, slightly atypical squamous epithelia (Figure 2, a–c), immature glands (Figure 2, e and f), immature hyaline cartilage, myxoid spindle cell stroma (Figure 2, a and e), and many interspersed blastemal/neuroectodermal areas (Figure 2, c and d) were also found. The last ones were formed by solid sheets of undifferentiated, monomorphic, small, round blue cells, with scant cytoplasm, hyperchromatic nuclei and numerous mitotic figures (5 to 20 mitoses/10 high-power fields) (Figure 2, c and d). Some of these blastemal-like areas proved to be of primitive neuroectodermal type presenting neuroepithelial rosettes (Figure 2e) or rare canalicular arrays mimicking the developing neural tube. The primitive neuroectodermal component occupied more than four histological low power fields (4× objective) on each slide, but each area was smaller than 5 mm diameter (one low power field, 4× objective) (Figure 2, c and d). The tumor infiltrated the nervous tissue.

The differentiation between the primitive neuroectodermal component and other embryonal tissues, especially immature glands was difficult, needing immunohistochemical stains. CD99 (Figure 3a), vimentin (Figure 3b), and β-catenin were diffusely positive in all primitive neuroectodermal components, β-catenin highlighting neuroepithelial rosettes (Figure 3c). These areas had a high proliferation index, as estimated by the immunoexpression of Ki67 of 60% (Figure 3d). Neuronal specific enolase (NSE) (Figure 4a), synaptophysin (Figure 4b), neurofilament and CD56 (Figure 4c) revealed focal areas of neuronal differentiation, inside or near the neuroectodermal areas or tubules. Pan-cytokeratin (CK) was positive in epithelial areas (Figure 4d), differentiating of these tissues from the neuroectodermal ones. Wilms' tumor (WT) marker for nephroblastoma-like differentiation was negative.

The proposed histological diagnosis was that of high-grade intracranial immature teratoma (grade III by the three-tiered Norris ovarian grading system) [5, 6]. On the other hand, the tumor relapse consisted mainly of a large primitive neuroectodermal component and in only small amounts of squamous and glandular epithelia, which attested the teratomatous origin of the tumor. The final diagnosis was that of a secondary malignant transformation or an overgrowth of a PNET malignant component in an already malignant immature teratoma.

After the histological diagnosis of intracranial immature teratoma with PNET overgrowth, the patient was further referred to the oncological team for adjuvant chemotherapy and radiotherapy. The treatment protocol for non-seminoma germ cell cancer was initiated. The first-line therapy included the use of Bleomycin–Etoposide–Cisplatin (BEP protocol), and the second the TIP protocol for relapsed testicular germ cell cancer, with Paclitaxel–Ifosfamide–Cisplatin, combined with external radiotherapy and after the relapse gamma-knife [7]. During the six years' follow-up, with repeated MRI brain scans, the patient presented full recovery, with no signs of relapse (2016).

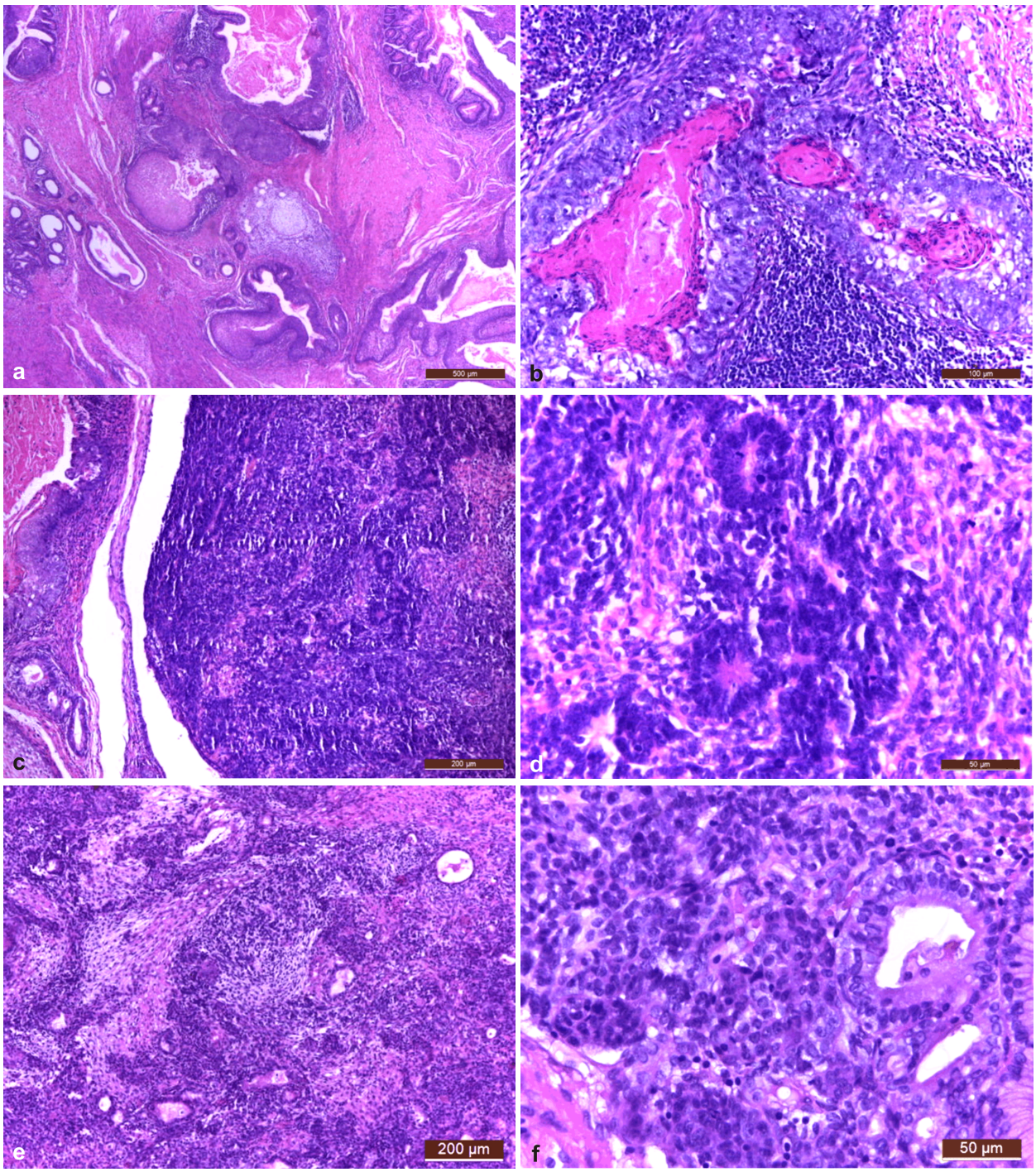

Figure 2 – ***The tumor presented a heterogeneous microscopic aspect: (a) A mixture of mature and immature epithelial and mesenchymal tissue; (b) Atypical squamous epithelia; (c) Solid neuroectodermal areas punctuated by rosettes; (d) Neuroepithelial rosettes; (e) Immature glandular area mixed with myxoid or dense stroma (HE staining, ×100); (f) Immature, mitotically active glands next to more mature glands. HE staining: (a) ×40; (c and e) ×100; (b) ×200; (d and f) ×400.***

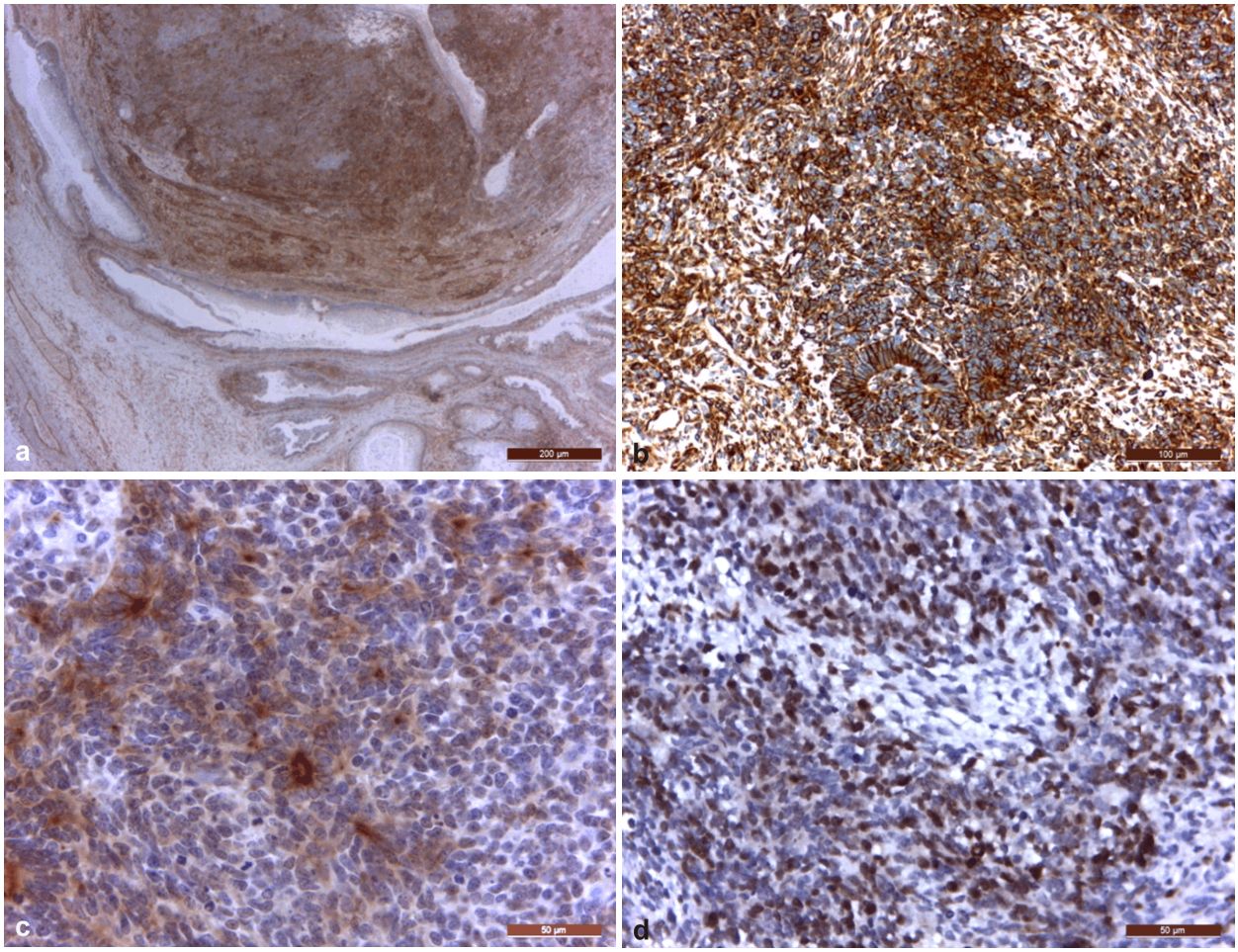

Figure 3 – ***Immunohistochemically, the solid neuroectodermal components were: (a) CD99 positive (×100); (b) Vimentin positive (×200); (c) Beta-catenin positive, especially in rosettes (×400); (d) Ki67 intensely positive (×400). Positivity is signaled by brown staining of the cytoplasm and/or nuclei.***

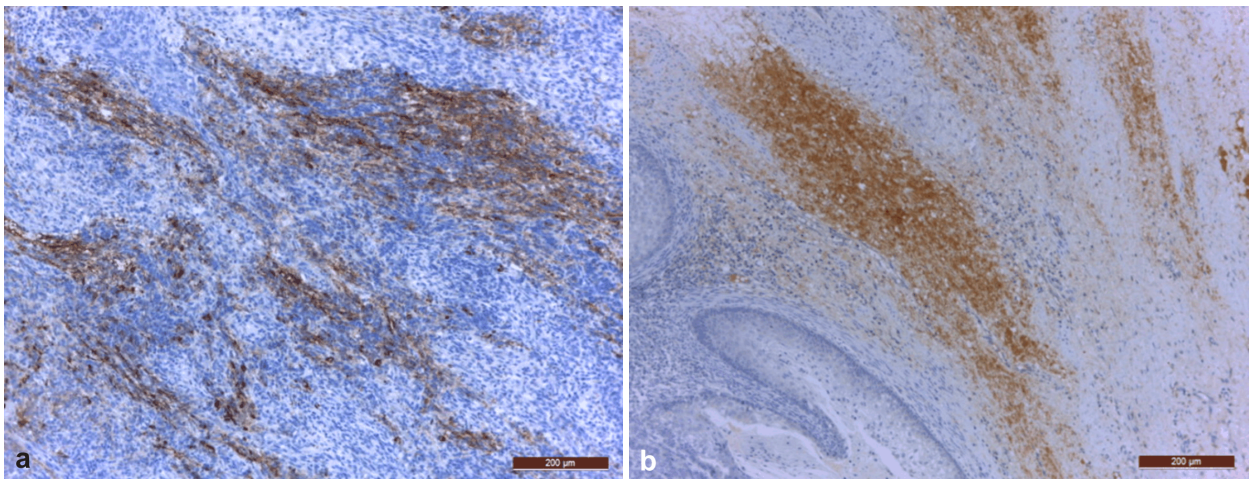

Figure 4 – ***Immunohistochemically, the tumor revealed: (a) Focal NSE99 positive areas (×100); (b) Focal synaptophysin positive areas (×100). Positivity is signaled by brown staining of the cytoplasm and/or nuclei.***

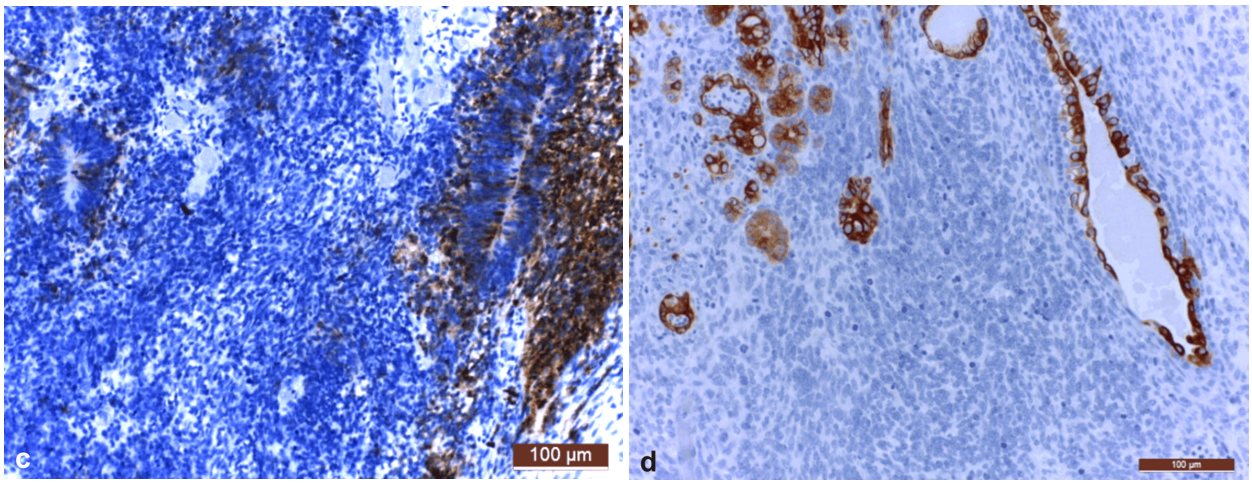

Figure 4 (continued) – ***Immunohistochemically, the tumor revealed: (c) CD56 positive area next to a neuroepithelial tubule (×200); (d) Pan-CK positive epithelia, merged to negative neuroectodermal component (×200). Positivity is signaled by brown staining of the cytoplasm and/or nuclei.***

Discussion

The immature intracranial teratomas are very rare tumors, with very few cases reported, particularly in adults. The histological diagnosis of an intracranial teratoma is usually a simple task, but the diagnosis of immaturity, and especially the presence of a secondary somatic malignant component may be sometimes difficult, even though critical for the management of the patient [3].

In the present case, the disorganized pattern of the multiple differentiation lines (endodermal mesodermal and ectodermal), the presence of immature stroma, cartilage and glands, the presence of focal atypia/dysplasia in the squamous epithelia, along with the presence of multiple blastemal areas, the majority of neuroepithelial type, rapidly oriented the diagnosis onto an immature intracranial teratoma.

Generally, the grading of an immature teratoma is not needed, with the exception of the ovarian ones. However, grading these tumors is helpful (irrespective of their sites), especially when immature components overgrow the original tumor (*e.g.*, PNET overgrowth, often difficult to be separated from a "high-grade" immature teratoma) [8]. In teratomas, the neuroectoderm is usually represented by neural tissue, glial tissue, ganglion cells, neuroepithelium, neuroblastic tissue or ocular structures [8]. Conventionally, the histological grading of the ovarian tumors is a semiquantitative analysis of the primitive and most aggressive part of the neuroectodermal component [5, 6]. The tumor grade is based on the aggregate amount and atypia of the foci of immature neuroectoderm present on any single slide [6, 8]. The immature neuroepithelial/neuroectodermal structures resemble those of the early embryonic central nervous system [4]. They are composed of neuroepithelial canals or tubules (particularly common), or of solid patterns punctuated by rosettes [3, 4]. The neuroepithelial tubules are small-sized, disorganized and mimic the developing early stage human neural tube; they are lined by stratified, overlapping hyperchromatic elongated cells, with numerous mitoses, without cilia but with slight protrusions abutting the lumen and with limiting external membrane [3, 5]. Outside the neuroepithelial tubules there are large fields, apparently stromal, which contain cells with neuroglial differentiation (neuronal, astrocytic or oligodendroglial one) [3]. In fact, as highlighted by Phi *et al.* (2007) active cell fate commitment and neuroglial differentiation take place within and around primitive neuroepithelial tubules [3]. The solid areas are hypercellular, with round cells and multiple rosettes, resembling PNETs [3]. According to the WHO (*World Health Organization*) two-tiered (or Norris three-tiered) grading system for ovarian immature teratoma, the tumor is of low grade (grade 1), when the amount of immature neuroepithelial tissue (tumors with rare foci) occupies less than one low-power (4× objective) magnification field in any single slide; the tumor is of high grade (grade 2 or 3) when the aggregate amount of immature neuroepithelial tissue occupies more than that, being larger than one low power (4× objective) magnification field in any slide [4]. Because immature and atypical neural components may overgrow, displaying various patterns of PNETs, the quantification of immature neuroepithelium on any single slide is of great importance; any monomorphic PNET-like proliferation (and not aggregate amount), which occupies at least one low-power field (4× objective, 5 mm in diameter) is considered an overgrowth, a somatic PNET type malignancy [4, 6, 8]. In the present case, after a thorough histological examination on HE-stained slides, the primary tumor corresponded to a high-grade immature teratoma, having any focus of PNET type proliferation larger than 5 mm diameter.

However, when other types of immature tissues are present, their differential diagnosis and their degree of immaturity and quantity must also be taken in consideration [6], a double simultaneous secondary overgrowth being also possible [4]. For example, nephroblastoma-type tissue, with an intermediate aggressiveness is sometimes encountered (true, more frequently in the testicular immature teratomas) [4, 9]. The blastemal component and the epithelial tubules present in nephroblastomas, or the immature glands as seen in this case, or the ependymal rosettes hamper the diagnosis and the grading of the neuroectodermal component. Therefore, a number of immunohistochemical markers are sometimes needed to discriminate the primitive components, especially the neuro-

epithelial ones, irrespective of tumor sites [4–6]. For immature neuroepithelium, the most potent markers are the pluripotency markers SOX2 and SALL4 (less specific than SOX2, revealing also the immature stroma or epithelial components) [3, 5, 8]. It is also revealed by glypican 3 (focally positive) and β-catenin [5, 8, 10]. The more differentiated neural areas are negative to weakly positive for the pluripotency markers, but they show a strong positivity to the characteristic neural markers such as vimentin, nestin, neural specific enolase, synaptophysin, neurofilament, CD56, glial fibrillary acidic protein and others, as was also demonstrated in this case [3, 8]. For the nephroblastoma type overgrowths, the WT1 nuclear intense positivity appears in all tumor cells (either blastemal, epithelial or stromal type), which were negative in this case [4, 8]. Alpha-fetoprotein (AFP) may staining immature gastrointestinal-type glands, as in this case. All these immunohistochemical markers usually demonstrate the same tissue or tumor specificity as in the original organs [4]. The reported case presented a high-grade histology (grade 3), having interspersed many primitive neuroepithelial areas between other components, each smaller than 5 mm diameter despite extensive immunohistochemical evaluation of the tumor.

Contrarily to literature data (the borderline or intermediate position occupied by immature teratomas in the biology of intracranial germ cell tumors), the patient presented a rapid recurrence. The histology of the second neoplasm corresponded to a somatic type malignancy of primitive neuroectodermal type. The higher malignancy was also suggested by the subarachnoid contralateral extension of the tumor. Given the heterogeneity of immature teratomas, the immature neuroepithelial component may be hazardously distributed, and sometimes confined to some part of the tumor, pattern that induces a risk of underdiagnosis caused by sampling error [3, 11, 12]. Alongside with the intracerebral infiltrative pattern, this may explain the rapid tumor recurrence seen in this case, though the biological progression induced by the high-grade histology itself may also be responsible factor.

The PNETs, which may appear in immature teratomas are heterogeneous somatic malignancies. As demonstrated by Ulbright *et al.* (2005) in testicular sites, very rare cases are of peripheral primitive neuroectodermal type, with specific chromosome 22 translocation, the majority sharing morphological characteristics with the CNS-PNETs (Homer Wright rosettes, ependymoblastic rosettes or medulloepithelioma-like papillary, tubular or trabecular arrangements) [1, 4, 5, 13]. However, for being considered the same distinct histogenetic diagnostic and therapeutic entity of CNS-PNETs as revealed by Spence *et al.* (2014), the morphological similarities must also have molecular-genetic support, which is not yet proved [14]. All secondary malignancies in teratomas are derivatives of the main tumor, of germinal cell origin. Some of them (fewer in intracranial location than in the testis), exhibit gain of 12p (usually as isochromosome 12p) as molecular signature [1]. These second malignancies add sometimes the new phenotype molecular characteristics and benefit of specific treatment, but this is yet to be proved for PNETs.

The genetic data of pure intracranial teratomas (of which 89% appear in males) proved differences between the congenital or infantile growths (with diploid status and general chromosomal integrity) and those beyond early childhood (with aneuploid profiles, complex chromosomal anomalies) [1]. These data parallel those of prepubertal testicular teratomas, now considered benign, and of peri- or post-pubertal testis, which are considered malignant, whether they are mature or immature [9]. This patient, as post-pubertal male, conformed well to this rule, highlighting the fact that regardless of the immaturity, any intracranial teratoma of post-pubertal males may be malignant. As in the testis, the presence of the PNET overgrowths has an unclear significance, since these tumors are already malignant [1, 9]. However, these overgrowths add a negative prognostic impact, as they seem to be usually chemoresistant to classic treatment protocols for germinal cell tumors [1, 9].

The treatment of teratomas with any type of malignant overgrowth is a challenge [11, 15]. The patients respond poorly to the cisplatin-based chemotherapy for conventional germinal cell tumors [4, 16], needing chemotherapy against the transformed component (described as having better results) [11, 16, 17]. The prognosis of these tumors depends on total surgical resection and combined radiochemotherapy [11, 17]. However, following a modern treatment for non-seminoma germ cell cancer, this patient had a good treatment response.

Conclusions

The present case highlighted the value of the WHO/Norris grading system (used in grading ovarian immature teratomas) in a very rare case of intracerebral immature teratoma, with an unexpected rapid subarachnoid extension of a PNET-like overgrowth. It also revealed the difficulties in current practice of histological diagnosis and grading of different immature tissues, especially of neuroectodermal origin. In spite of the fact that the diagnosis of an intracranial immature teratoma is usually a simple task, these structures need sometimes immunohistochemical stains to differentiate them from other immature elements of epithelial or mesenchymal type.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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