A pseudo-endocrine suprasellar tumour: review of primitive neuroectodermal tumours in adults

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Abstract

Primitive neuroectodermal tumours (PNETs) are very rare malignant brain tumours mostly affecting children. We report a 55-year-old female with a PNET, presenting with the clinical picture of a large suprasellar tumour. The patient complained of visual field defects, and had personality changes but no endocrine deficiencies or signs of hypothalamic disturbance. The diagnosis of craniopharyngioma was initially suspected on computerised tomography scan, but was not confirmed by magnetic resonance imaging, because of the presence of some perilesional oedema. The tumour was removed in two phases: first through a right frontal craniotomy to remove the suprasellar part and two weeks later through a transsphenoidal approach to remove tumour tissue from the sella turcica. The pathological examination of the first resected specimen revealed compact fields of small, rounded cells and hyperplasia of the interstitial connective tissue, compatible with an adamantinomatous craniopharyngioma. Pathological investigation after the second operation demonstrated perivascular pseudo-rosettes and immunoreactivity of tumour cells for synaptophysin, favouring the diagnosis of a PNET. After the surgery the patient retained a serious cognitive deficit. Staging examinations were not performed and the intention of systemic therapy was abandoned. She died six months later, in poor general condition, of a respiratory infection. Our case of PNET is the first to be reported with a suprasellar location in an adult patient and we suggest that this diagnosis should be included in the differential diagnosis of a hypothalamic tumour in adults. The epidemiology and therapy of this unusual type of tumour is reviewed in detail.
The patient quarrelled with her neighbours. The patient acknowledged only dizziness and some visual disturbance. On physical examination, the patient appeared normally oriented but disinhibited. The acuity of the right eye was approximately found to be decreased, but other neurological deficiencies were not apparent.

A diffuse increase of theta waves on an electroencephalogram was interpreted as indicative of ‘general cerebral dysfunction’. On X-ray, the sella turcica appeared to be grossly enlarged and the dorsum was eroded. A brain computerised tomography (CT) scan showed a 60 mm large, partially calcified tumour, which was located above the sella turcica, suggestive of a craniopharyngioma. Magnetic resonance (MR) examination demonstrated a large tumour with enclosed cysts, extending into the sphenoid sinus and compressing the cavernous sinus (Fig. 1). Comparable sizes of suprasellar and intrasellar parts of the tumour and a shell of perilesional oedema were noted to be less characteristic of a craniopharyngioma (Fig. 2).

Eye examination indicated a normal fundus but a diminished visual acuity at the right side (right side 2/10 as compared with left side 10/10). In the right visual field a central scotoma and normal peripheral borders were noticed. Hormonal determinations showed a normal thyroid function and gonadotrophin levels in accordance with a post-menopausal state. Prolactin and growth hormone levels appeared to be within normal limits. The morning serum cortisol level and 24-h urinary cortisol excretion were found to be elevated to 1090 nmol/l (normal levels 166-773 nmol/l) and 993 nmol/day (normal excretion 110-440 nmol/day) respectively. These abnormal values were still considered to be compatible with a physiological reaction to stress. Furthermore, the basal adrenocorticotrophin level was within normal limits.

The first operation, which lasted 15 h, was performed through a right frontal craniotomy. The tumour appeared to be tender, but enclosed by a firm capsule. It contained several cysts, filled with a crystalloid material. As large as 6 cm in diameter, it had surrounded both internal carotid arteries and had bifurcations into the anterior and middle cerebral arteries, the optic chiasm and both optic nerves. Since complete debulking of the sella turcica was not feasible, it was decided to remove the tumour intra-capsularly and to perform a second operation through a
transsphenoidal approach. Light microscopic examination showed an adamantinomatous craniopharyngioma, consisting of compact fields of cells with a basaloid appearance and interstitial strips of hyaline connective tissue. Dystrophic lime appeared in the form of psammoma bodies next to clefts of washed out lipids.

The second operation, through a transsphenoidal approach, was performed 2 weeks later as the clinical picture had not improved in the meantime. The well vascularised tumour was shown to fill up the sphenoid sinus. Light microscopical examination showed a dense population of small, rounded cells located as pseudo-rosettes around blood vessels. Iron-laden macrophages and extracellular deposits of orange-brown iron pigment were noted. The central oval cell nuclei contained chromatin with a salt-and-pepper appearance and only small nucleoli. Even though only a limited number of mitoses were found at light microscopical examination, a Ki-67 immunohistochemical study showed a labelling index of about 10%. Immunohistochemical examination showed immunoreactivity for neuron specific enolase (NSE), synaptophysin and chromogranin, but not for neurofilament protein (NFP) or glial fibrillary acid protein (GFAP), and for none of the pituitary hormones (Figs 3 and 4). All these findings were suggestive of a small-cell, malignant tumour with neuroendocrine differentiation. The preferential diagnosis was a primitive neuroectodermal tumour (PNET) of cerebral origin, with break-through in the sphenoid sinus. The first tentative diagnosis of craniopharyngioma was therefore considered to be incorrect, probably due to inadequate tissue sampling.

After the operation, the patient presented a panhypopituitarism and a substitution treatment with hydrocortisone (30 mg/day), levothyroxine (50 µg/day) and desmopressin acetate (2 × 15 µg intranasally) was started. A brain CT scan one month after the operation demonstrated a hypodense and inhomogeneous aspect of the tissue in the right frontal lobe, with limited contrast uptake, indicating local oedema as a postoperative sequel. A foggy appearance of the sphenoid sinus and a large amount of air in the sella turcica, perimesencephalic cisterns and in both lateral ventricles were strongly suggestive of a ventriculo-sphenoidal fistula, which could explain the clinical finding of cerebrospinal fluid leakage from the nose. In addition, the broadening of both lateral ventricles was a clear sign of postoperative hydrocephalus. A reconstruction of the skull base was therefore attempted and led to the closure of the fluid leak through a small opening in the bottom of the sella turcica.

An ophthalmological examination was repeated after the operation but appeared invalid because of lack of cooperation from the patient. Neurolinguistic evaluation pointed first to a postoperative confusional state and, later, as deficits in memory and frontal functions became more apparent, to a demential syndrome. This was an additional reason not to perform the usual staging examinations and to postpone radiotherapy until a better general state would have been attained. Moreover, in close consultation with her family, the patient was admitted to a long-term care.

**Figure 3** Light microscopic examination shows a dense population of small, rounded cells located as pseudo-rosettes around blood vessels (arrows). The central oval nuclei contain chromatin with a salt-and-pepper appearance and only small nucleoli. The number of mitoses is limited. Immunohistochemical staining for NSE; original magnification: objective ×40, ocular ×10.

**Figure 4** Immunohistochemical examination shows immunoreactivity for synaptophysin. Original magnification: objective ×40, ocular ×10.
facility. There she died of an intercurrent respiratory infection about six months after the operations.

**Discussion**

**Definition**

The definition of PNET has been a point of debate for a long time (Tomita et al. 1988, Pigott et al. 1990, Robles et al. 1992). Hart and Earle (1973) introduced the term PNET to describe largely undifferentiated neoplasms occurring in the cerebrum of young individuals and consisting of more than 90% of undifferentiated cells resembling the germinal matrix cells of the embryonic neural tube. Up to 10% of the tumour cells may exhibit evidence of differentiation along either neuronal or glial lines. Nevertheless, Rubinstein (1985) argued in favour of a classification of embryonic central nervous system (CNS) tumours according to the stages of cytogenesis: medulloepithelioma (neural tube cells), neuroblastoma (primitive neurones), polar spongioblastoma (primitive astrocytes) and ependymoblastoma (ependymal cells). Even though, traditionally, a distinction is made between neuroblastoma (cerebrum), medulloblastoma (cerebellum), pineoblastoma (pineal gland) and retinoblastoma (retina), Rorke et al. (1985) advocated a more general application of the term PNET irrespective of tumour localisation. Embryonic CNS tumours, consisting of less than 90% of undifferentiated cells and arising above the tentorium (i.e. not in the cerebellum) in patients of all ages, may thus be classified as PNET (Gaffney et al. 1985).

PNETs resemble classical medulloblastomas in several respects, such as histological appearance, occurrence in children and malignant behaviour (Gaffney et al. 1985). Apart from the localisation respectively above and below the tentorium, differences between these two tumours consist of the most prevalent type of cell differentiation (astrocytic in PNETs vs neuronal in medulloblastomas), the capacity to seed along the cerebrospinal axis (15% vs 50%) (Albright et al. 1995), and the response to surgical and radiation therapy (25% vs 50% 5-year survival rate) (Gaffney et al. 1985). In addition, there are arguments in favour of different genetic effects involved in the aetiology of the two tumour types (e.g. chromosome arm 17p deletion exclusively in medulloblastomas and not in PNETs) (Burnett et al. 1997).

**Epidemiology**

The information on the incidence of PNETs is usually reported in conjunction with that of medulloblastomas. In children the occurrence of PNETs is estimated at 3% of all brain tumours, as opposed to 25% for medulloblastomas (Albright et al. 1995, Dirks et al. 1996). In adult patients the occurrence of PNETs is believed to be less than 10% that of medulloblastomas (Peterson & Walker 1995). The overall incidence of PNETs is estimated at 0.06/100 000 person/years (Grant et al. 1988). Eighty percent of all patients with either a PNET or medulloblastoma are less than 15 years of age (Albright et al. 1995, Peterson & Walker 1995). All in all, only 35 adult patients with a PNET have been reported in the literature (Bellis et al. 1983, Gaffney et al. 1985, Kuratsu et al. 1986, Shuangshoti 1986, Grant et al. 1988, Louis & Hochberg 1990, Pigott et al. 1990, Louwaeghe et al. 1993, Miyazawa et al. 1994, Selassie et al. 1994, Papiernik et al. 1995, Peterson & Walker 1995, Pickuth & Leutloff 1996).

Whereas PNETs are most often located in frontal and parietal lobes (Altman et al. 1985, Gaffney et al. 1985, Grant et al. 1988, Tomita et al. 1988, Robles et al. 1992, Albright et al. 1995, Dirks et al. 1996), about 10% of the tumours are found around the third ventricle (Grant et al. 1988). PNETs with a suprasellar location have been reported previously only in children, either occurring in association with a retinoblastoma, as part of a so-called ‘trilateral retinoblastoma’ (in about 10 patients) (Bejjani et al. 1996), or isolated (in 4 patients) (Altman et al. 1985, Kingston et al. 1985, Tomita et al. 1988). These suprasellar tumours generally extend into the cerebral hemispheres and not into the sella turcica as in our case.

**Aetiology**

In the World Health Organisation classification of CNS neoplasms, PNETs are grouped as embryonic tumours because of the resemblance of tumour cells to primitive, undifferentiated neuroepithelial precursor cells (Tatter et al. 1996). Retinoblastomas are also regarded as a sort of embryonic CNS tumour, closely related to PNETs (Bejjani et al. 1996). In the sporadic as well as hereditary cases of this tumour, a mutation is assumed in both alleles of the retinoblastoma tumour suppressor gene, located on chromosome 13q14. The deficient gene product acts as a negative regulator of the transcription factors that are responsible for the entry of retinal precursor cells into the DNA synthesis phase of the cell cycle (Tatter et al. 1996). For PNETs a similar ‘PNET tumour suppressor gene’ may be assumed, the mutation or deletion of which would allow the malignant transformation of neuroepithelial cells at the different stages of differentiation: neural tube cells, neuroblasts, spongioblasts or ependymal cells (Robles et al. 1992). However, up to now no single gene has been mapped for PNETs and translocations or additions can be demonstrated, but no consistent deletions have been found which would support the hypothesis of tumour suppressor gene loss (Pigott et al. 1990).
Pathology
Macroscopically, PNETs are large (7 cm in diameter on average) soft, grey-white masses, with prominent cystic and variable haemorrhagic components. The tumours are sharply delineated, enclosed by a pseudo-capsule even though they appear microscopically invasive (Gaffney et al. 1985, Robles et al. 1992).

Light microscopically, the tumours consist predominantly of small, undifferentiated cells with ovoid hyperchromatic nuclei and a high nucleo-cytoplasmic ratio against a fine fibrillary background. Mitoses are often abundantly present, whereas areas of necrosis, haemorrhage and calcification can occur to a variable degree within the tumour (Gaffney et al. 1985, Grant et al. 1988, Robles et al. 1992). In practice, the proportion of differentiated cells can range from 0% to more than 20% of all tumour cells (Gaffney et al. 1985, Pigott et al. 1990). PNETs lacking any evidence of differentiation are actually very rare and may be considered as a special subtype (NOS=not otherwise specified) (Miyazawa et al. 1994). On the other hand, if differentiated tumour cells are present, often more than one type of differentiation is represented within a single tumour (Gaffney et al. 1985). On the basis of light microscopy, tumour cells show evidence of astrocytic, neuronal and oligodendrocytic differentiation in, respectively, 61%, 50% and 39% of the cases, whereas ependymal differentiation is quite uncommon (6%) (Gaffney et al. 1985). When cells with neuronal differentiation predominate among differentiated tumour cells and the PNET would thus histologically be classified as a neuroblastoma, a desmoplastic variant can be distinguished if concomitant hyperplasia of the connective tissue stroma is present (Robles et al. 1992, Tatter et al. 1996). Furthermore, perivascular pseudo-rosettes are considered to be a hallmark of ependymal differentiation (Gaffney et al. 1985).

By means of electron microscopy, characteristics of neuronal differentiation (neurites, neuritubules, dense-core vesicles, ...) can be demonstrated in a majority of PNETs (70-87%) (Pigott et al. 1990, Papierz et al. 1995). Immunohistochemistry also can indicate differentiation in areas of apparent morphological uniformity (Papierz et al. 1995). Evidence of neuronal differentiation, such as immunoreactivity for synaptophysin or NFP, can be shown in a highly variable proportion of PNETs: 0-12% up to 91% (Grant et al. 1988, Pigott et al. 1990, Papierz et al. 1995). Immunoreactivity for GFAP can be demonstrated in 87-92% of the tumours, indicating entrapped stromal astrocytes or astrocytic differentiation of tumour cells (Gaffney et al. 1985, Grant et al. 1988, Pigott et al. 1990, Papierz et al. 1995). On the other hand, a particular differentiation for NSE or S-100 protein cannot easily be gathered from immunoreactivity, because of lack of specificity of these markers (Grant et al. 1988, Papierz et al. 1995). Another purpose of immunohistochemistry is to aid the distinction from other types of CNS tumours: undifferentiated secondary tumours, poorly differentiated small-cell tumours native to the CNS (e.g. germinomas, lymphomas or choroid plexus carcinomas) (Gaffney et al. 1985, Grant et al. 1988, Pigott et al. 1990), or a pituitary adenoma as in our case. Furthermore, the cell proliferation index derived from a Ki-67 immunohistochemical study (range 1-13% for PNETs) may provide additional prognostic information (Bodey et al. 1997). In our case, the first biopsy had already shown a hyperplasia of the connective tissue stroma, but only the second biopsy demonstrated perivascular pseudo-rosettes and an immunoreactivity of tumour cells for synaptophysin, but not for NFP or GFAP. These findings may indicate some degree of neuronal and ependymal differentiation within the PNET.

Symptoms
Patients of all ages may present with a clinical picture consisting of symptoms and signs of raised intracranial pressure. In children, these appear as increasing listlessness, nausea, vomiting, while in adults headache, visual disturbances and possibly epilepsy are more prominent. The history of the illness is usually relatively short, between one week and three months (Pigott et al. 1990). Apart from changes in personality, our patient also presented with visual field loss due to the suprasellar location of the tumour. Endocrine deficiencies were not clinically or biochemically apparent.

Radiology
Radiography of the skull, when performed in patients with PNET, can show calvarial asymmetry or bone erosions (Robles et al. 1992). On CT scan a PNET appears as a heterogeneous, iso- to hyperdense mass, containing areas of calcification and cysts, with little surrounding oedema (Altman et al. 1985, Pigott et al. 1990, Robles et al. 1992, Pickuth & Leutloff 1996). Although PNET can occasionally present as an intracerebral haemorrhage (Louwaege et al. 1993), bleeding within a tumour is not as readily distinguished by CT scan (Figueroa et al. 1989, Pickuth & Leutloff 1996). Contrast enhancement is heterogeneous and generally demonstrates well-defined margins. Mass effect and/or hydrocephalus can easily be recognised on CT scan (Altman et al. 1985, Pigott et al. 1990, Robles et al. 1992, Pickuth & Leutloff 1996). At MR examination, PNETs exhibit characteristics similar to those on CT scan, except of course for hypointensity on T1- and hyperintensity on T2-weighted images (Figueroa et al. 1989, Robles et al. 1992, Louwaege et al. 1993, Pickuth & Leutloff 1996). Whereas MR imaging in general is thought to provide a better anatomical definition.
of tumour margins, the haemorrhagic component of PNETs is most apparent on T1-weighted and the lack of significant surrounding oedema on T2-weighted images (Figueroa et al. 1989, Robles et al. 1992, Pickuth & Leutloff 1996). In addition, MR imaging allows a better detection of intracerebral, subarachnoidal and meningeal metastases. From the latter stems the need for an MR examination of the spinal cord in tumour staging (Robles et al. 1992, Pickuth & Leutloff 1996). Initial staging of PNETs should furthermore include an examination of the cerebrospinal fluid, but no routine systemic imaging in asymptomatic patients (chest X-ray, echography of the abdomen, whole body bone scan, ...), because of the negligible prevalence of extraneural metastases at the time of diagnosis (Peterson & Walker 1995). In our case, a craniopharyngioma was suspected on CT scan, because of the location of a heterogeneous mass mainly above and within the sella turcica. At MR examination, the presence of some surrounding oedema was noted as an argument against craniopharyngioma (Hald et al. 1995), but this was not immediately suggestive of a PNET. In the literature only one case has been reported of a suprasellar PNET that was suspected preoperatively by means of imaging techniques (Altman et al. 1985).

**Therapy**

Many authors argue in favour of a multimodal radical treatment, which allows for a systemic therapy from the outset (Bellis et al. 1983, Gaffney et al. 1985, Tomita et al. 1988, Albright et al. 1995, Peterson & Walker 1995, Dirks et al. 1996). An optimal treatment regimen is not yet established because of a lack of clinical trials due to the very low incidence of PNET (Peterson & Walker 1995). Total tumour excision on its own has been shown to enhance survival in two reports (Gaffney et al. 1985, Dirks et al. 1996), or to reduce local recurrence without influencing survival in another report (Tomita et al. 1988). A major argument in favour of early systemic therapy is that (intraneural) metastases, which are difficult to demonstrate at the time of diagnosis (in 5-15% of patients), are abundantly present in the end stage of the disease (in 45-100%) (Gaffney et al. 1985, Tomita et al. 1988, Albright et al. 1995, Dirks et al. 1996), whereas local recurrence after tumour excision can only be found in 45-50% of end stage patients (Gaffney et al. 1985, Tomita et al. 1988). Although PNETs are generally considered to be less radiosensitive than medulloblastomas, tumour excision is often combined with neuraxis irradiation, because of some separate reports of unusual long survival and low morbidity (Gaffney et al. 1985). A dose and duration of irradiation to the primary tumour site of 30-35 Gy and 5 weeks respectively have been recommended, whereas these figures for irradiation to the spinal cord amount to 30-35 Gy and 5 weeks (Gaffney et al. 1985). For the use of chemotherapy in the treatment of PNET three indications may be considered: (1) palliative treatment, (2) holding measure to delay the need for radiotherapy in children under the age of three years and (3) adjuvant chemotherapy (Gaze et al. 1994). With the combination of nitrosourea and vincristine, some individual cases of unusually long survival have been reported (7-11 years) (Gaffney et al. 1985) whereas, in general, no significantly longer survival arose with adjuvant chemotherapy compared with treatment regimens without adjuvant chemotherapy (Tomita et al. 1988, Dirks et al. 1996). The combination of vincristine, cyclophosphamide, carboplatin and etoposide (e.g. according to the adapted International Society of Paediatric Oncology and UK Children’s Cancer Study Group III (SIOP-UKCCSG III) protocol)) has been shown to involve a high response rate (85%), a long time to relapse and relatively low toxicity (Gaze et al. 1994). As a result, the palliative setting is considered to be a good indication for this type of chemotherapy (Gaze et al. 1994). In our case, no systemic therapy was applied in consultation with the patient's family, given the state of dementia after tumour resection.

**Prognosis**

Survival rates after tumour excision and neuraxis irradiation (and in some cases adjuvant chemotherapy) are reported to be as high as 37-64% survival at 1 year, 12-50% survival at 2 years and 6-33% survival at 5 years. The average survival period has been estimated at 10-37 months (Altman et al. 1985, Gaffney et al. 1985, Grant et al. 1988, Tomita et al. 1988, Pigott et al. 1990, Albright et al. 1995, Dirks et al. 1996, Pickuth & Leutloff 1996). PNETs are generally acknowledged to involve a poorer prognosis compared with medulloblastomas (Gaffney et al. 1985, Tomita et al. 1988, Gaze et al. 1994, Albright et al. 1995, Peterson & Walker 1995, Dirks et al. 1996). Figures for 5-year survival rate after multimodal treatment differ by as much as 25% and 50% (Gaffney et al. 1985). PNETs are claimed to entail a poorer prognosis in adults as compared with children. In one report the 5-year survival rate for adults is estimated at 14% (Gaffney et al. 1985), whereas in another report considering only children a 5-year survival rate of 33% is mentioned (Albright et al. 1995). Conversely, age less than three years is also associated with a poorer prognosis, mainly because of the contraindication for radiotherapy (Albright et al. 1995, Dirks et al. 1996). Apart from age, the proportion of differentiated cells within a PNET is another useful prognostic factor (longer survival if more than 10% of tumour cells are differentiated) (Gaffney et al. 1985). Survival does not appear to be dependent on the type of
differentiation (neuronal or glial) (Tomita et al. 1988, Albright et al. 1995, Dirks et al. 1996). A last important indicator of poor prognosis is the presence of metastases at the initial staging (Albright et al. 1995), which can actually be found in 5-15% of the patients as mentioned above (Gaffney et al. 1985, Tomita et al. 1988, Albright et al. 1995).

References


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