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Pathology in Focus

Peripheral primitive neuroectodermal tumour (pPNET) of the cerebellopontine angle presenting in adult life

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Abstract
We report a case of a peripheral neuroectodermal tumour (pPNET) of the cerebellopontine angle of a 67-year-old woman. The patient's age at presentation was highly unusual. This case highlights the difficulties encountered, both clinically and pathologically, in securing the correct diagnosis of such a rare condition presenting in this relatively inaccessible area. The development of the nomenclature and classification of neuroectodermal tumours is traced. Recent advances in immunohistochemistry and genetic typing have shown the close relationship between pPNET and the previously difficult to classify Ewing's sarcoma and Askin's tumour.

Key words: Neuroectodermal Tumours, Primitive; Cerebellopontine Angle; Adult

Introduction

The concept of the primitive neuroectodermal tumour (PNET) was introduced in 1973 in an attempt to help classify an unusual group of undifferentiated brain tumours.[1] These were highly malignant small cell neoplasms found mainly in children and young adults.[2] Supratentorial PNETs were morphologically identical to the well-documented medulloblastoma tumours (PNET/MB) which, by definition, only occur in the posterior fossa. Together they constitute the most common childhood brain neoplasms, accounting for 20 per cent of all cases.[3] Cases presenting in adults are, in contrast, rare.[4] Since in 90–95 per cent of cases these tumours were undifferentiated, the concept of the PNET was thought to be helpful as it stressed the primitive nature of the tumours and did not rely on theories of histogenesis for classification. Rorke *et al.* expanded this theory to include other, previously well-documented, often more differentiated, tumours elsewhere in the brain and spine and even outside the CNS.[5] Examples of these include pineoblastoma, ependymoblastoma and retinoblastoma. It was postulated that all were derived from a putative multipotential cell from the primitive neural tube and thus should come under a common classification. Over time the nomenclature has become somewhat confused, with various authors developing their own slightly differing classifications.[6–8]

The concept of the PNET was not fully accepted by all authorities. One of the main critics was Rubenstein who thought this was a 'simplistic' way of thinking and felt that such distinct pathological entities as pineoblastoma, ependymoblastoma or retinoblastoma should not be classified under the single blanket term of PNET.[9] His view was more in keeping with the sentiments of Hart and Earle in their original paper in which they suggested that the term PNET should be applied to largely undifferentiated tumours.[1]

In a more recent review of the current literature of this controversial field Dehner has given support to the PNET theory but has proposed that a differentiation be made between *central* PNETs originating in the central nervous system and *peripheral* PNETs which do not.[10] A degree of clarification also came in 1993 with the World Health Organisation's new classification of intracranial tumours.[11]

The prognosis for all patients with these conditions is uniformly poor regardless of type of treatment offered, whether surgery, radiotherapy or combined chemotherapy.[12,13]

We present a case of PNET found in an elderly female which is unusual in both its site and the age of the patient at presentation. We discuss the clinical and pathological features of these tumours.

Case report

A 67-year-old lady presented following an 18-month history of right-sided stabbing facial pain. She had noticed progressive weakness of the facial muscles on that side for seven months and latterly there had been a deterioration of the hearing on the right side together with some headache. She had begun to slur her speech.

Cranial nerve examination revealed several abnormalities on the right side: decreased sensation was present in all divisions of the trigeminal nerve; the corneal reflex was sluggish and there was a House-Brackman grade IV facial weakness with some drooling of saliva. The other cranial nerves were intact. Direction changing and vertical nystagmus was observed. Saccadic pursuit was present to

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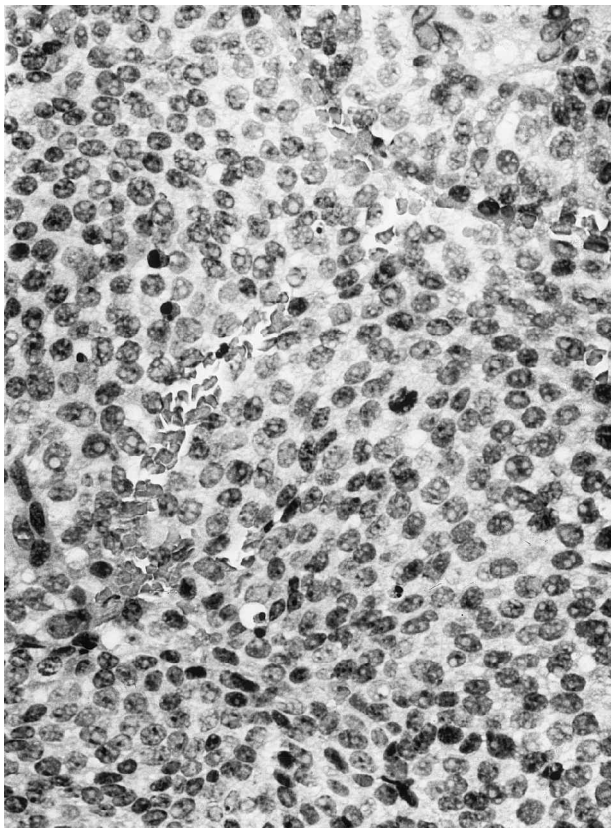

FIG. 1
Sheets of small round or oval cells with hyperchromatic nuclei and scanty cytoplasm (H & E; ×300)

both sides, especially on right gaze. Romberg's balance test was negative but she fell to the right when attempting Unterberg's stepping test. Her gait was ataxic. Although she was mildly dysarthric, formal tests of co-ordination were completed without trouble. Pure-tone audiometry showed asymmetry, with a 50 dB sensorineural hearing level on the right. General physical examination including fibre-optic examination of the upper aero-digestive tract was unremarkable. The clinical impression was that this was not a vestibular schwannoma.

T1-weighted magnetic resonance imaging (MRI) showed a mass lesion of the right cerebellopontine angle (CPA) extending into the internal auditory meatus. Post-gadolinium contrast administration there was patchy enhancement of the lesion which was not thought to be typical of a vestibular schwannoma. At surgery, via a retrolabyrinthine approach, a mass was seen to be arising from the VIIIth cranial nerve in the cerebellopontine angle. Biopsy specimens were taken. Recovery was unremarkable. The initial histological assessment suggested an epithelial neoplasm infiltrating nerve tissue, with the latter showing a degree of schwannosis. The tumour cells were small, fairly uniform and arranged in sheets (Figure 1). The cells contained round or oval hyperchromatic nuclei with inconspicuous nucleoli and scanty cytoplasm. No rosettes were seen. Prominent stromal blood vessels were noted in places. Apoptosis was present but only occasional mitoses were seen. Immunohistochemical staining showed the cells to be positive to neurone-specific enolase (NSE) and chromogranin. Stains for epithelial markers CAM5.2 and AE1/AE3 were negative. Leukocyte common antigen (CD 45) was not detected. These findings suggested a

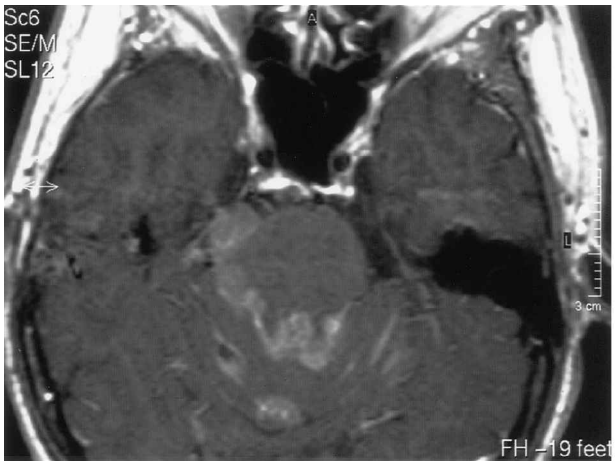

FIG. 2(a)
T1, gadolinium-enhanced, MR image showing residual CPA tumour with extension into the fourth ventricle. Subarachnoid space spread is shown with infilling of the folia of the cerebellum.

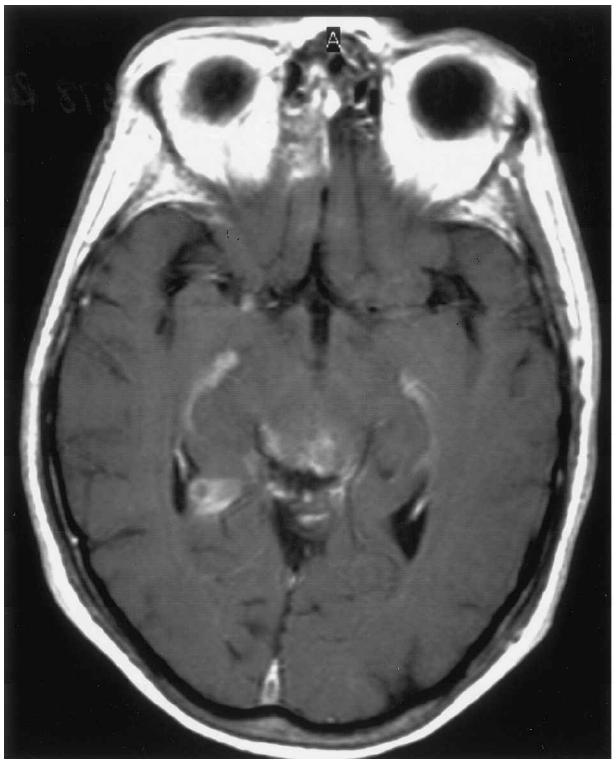

FIG. 2(b)
T1, gadolinium-enhanced, MR image showing multiple metastases.

neuroepithelial/neuroendocrine origin for the neoplasm and because nerve tissue was being invaded it was thought that this CPA lesion might be a metastatic deposit. Possible primary tumours considered included small cell carcinoma of lung, spread from a nasopharyngeal neuroendocrine tumour or spread from metastatic carcinoid.

Further efforts to identify a possible primary neuroendocrine source for the tumour were made. A chest X-ray and computed tomography (CT) scan of the head, neck, thorax and pelvis were negative. Radioactive iodine-123 MIBG whole-body scanning was equivocal. A suggestion of increased uptake in the region of the adrenal glands was

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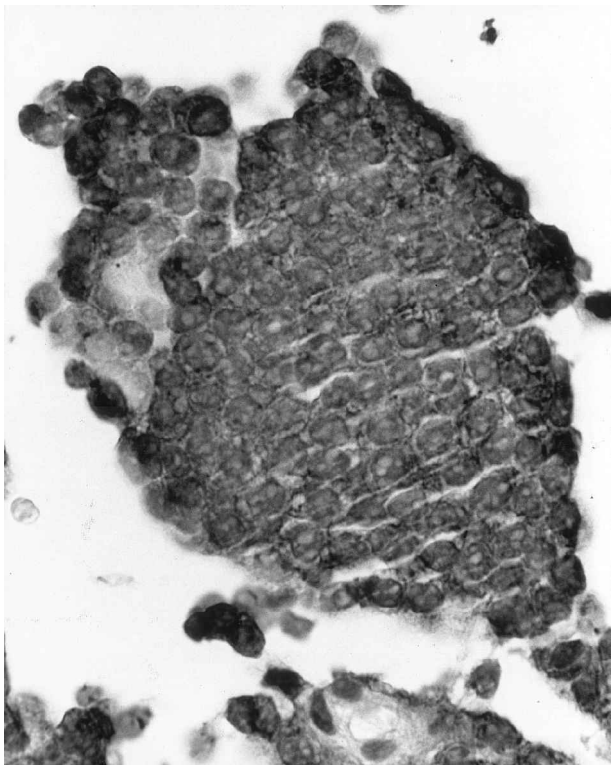

FIG. 3
Synaptophysin positivity in the tumour cells (Avidin-biotin-peroxidase method; ×380)

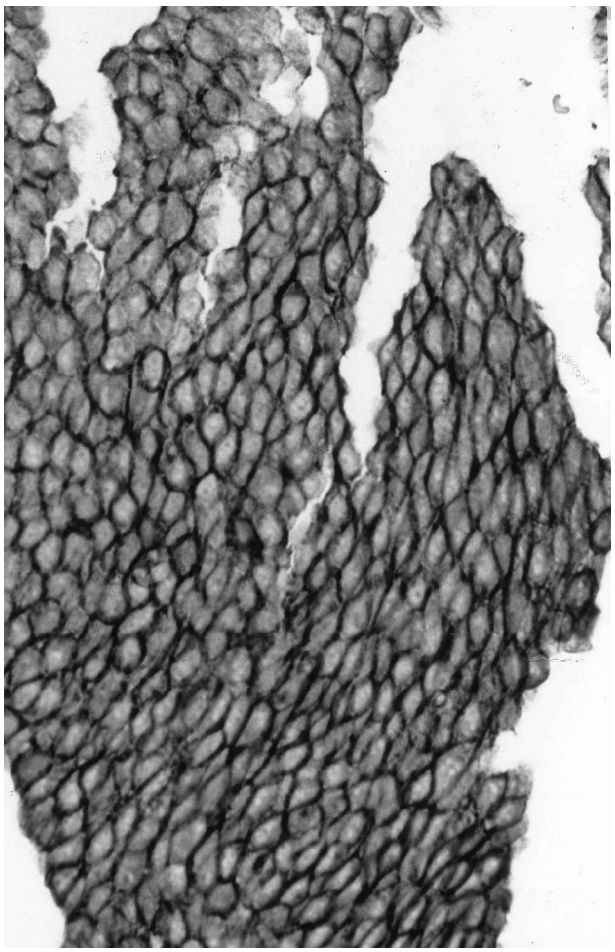

FIG. 4
Immunostaining for Beta-2-microglobulin (×300)

present but was insufficient to confirm the presence of an adrenal tumour. A somatostatin receptor scan did not confirm the findings of the first isotope study but did show increased uptake in two areas in the skull, one in the region of the CPA and the other in the region of the pituitary and also extending across the midline. A repeat MR scan showed the original tumour in the right CPA cistern but now with extension through the right foramen of Luschka into the fourth ventricle (Figure 2). Further tumour deposits were seen in the third ventricle and right lateral ventricle. Tumour was also seen in the sub-arachnoid space.

The histological samples were sent to the regional cancer centre for review. Further immunohistochemical studies were carried out. The tumour cells again showed positivity for NSE, synaptophysin (Figure 3) and focally for chromogranin. Occasional cells were positive for neurofilament protein. Staining for Beta-2 microglobulin was strong (Figure 4) and there was also membranous MIC 2 (CD 99) staining (Figure 5). Stains for cytokeratin, EMA, desmin, SMA and GFAP were negative. Stain for S100 protein showed trapped nerve fibres in the tumour. These findings are in keeping with a diagnosis of peripheral neuroectodermal tumour (PNET).

The patient underwent palliative cranial irradiation and survived with no progression of her symptoms for 13 months after presentation. This was followed by rapid decline and death.

Discussion

The concept of the PNET is useful as it helps with the classification of various morphologically similar tumours and originally dispensed with the necessity to postulate

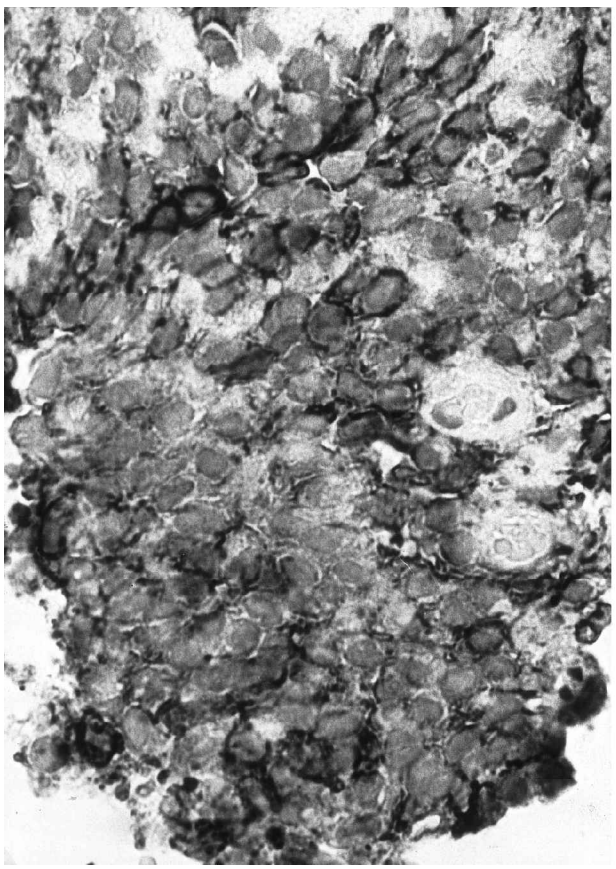

FIG. 5
Immunostaining for MIC 2 (×380)

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their histogenesis. The term has gained support despite suggestions in some quarters that it lacks conceptual validity. Dehner has argued that there may be a group of histologically similar neoplasms 'expressing some of the morphological attributes of the germinal neuroepithelium and/or the neural crest of the developing nervous system'.[10] A distinction is made between *central* PNETs found in the brain or spinal cord and *peripheral* PNETs (pPNETs) found outside the CNS.

Whilst the adrenal and extra-adrenal neuroblastoma may be considered as the classic peripheral PNET, other small-cell neurogenic tumours of the soft tissues, nerves and bones, described previously in the literature as peripheral neuroepithelioma, neuroblastoma or medulloepithelioma, are also included. The nomenclature also allows accommodation of the previously difficult to classify Askin's tumour (a malignant small-cell tumour of the thoraco-pulmonary region) and Ewing's sarcoma.[10] The ability of the neural tube cells to differentiate along both neural and mesenchymal lines should not be forgotten when trying to understand how such a disparate group of neoplasms may have originated from a common precursor cell.[14]

The first description of a peripheral neuroepithelial tumour was made in 1918 by Stout who observed a tumour of the ulnar nerve.[15] Since that time, in addition to the well-known tumours mentioned already, pPNETs have been reported in many sites including the ovary, neck, retroperitoneum, skin and soft tissues.[16] One previous case of PNET in the CPA has been reported which was only diagnosed in retrospect one year after the failure of stereotactic radiosurgery for what had originally been diagnosed radiologically as a vestibular schwannoma. In this report no distinction is made between central or peripheral PNET.[17] The symptoms of these tumours at presentation obviously depends upon their site. PNETs are predominantly tumours of childhood and young adults: In a study of 54 extracranial PNETs presenting over a period of 20 years to the Memorial Sloane-Kettering Hospital only 10 per cent were in patients over the age of 40 years, with the median age at presentation being 17 years.[18]

Macroscopically these tumours tend to be well-circumscribed, often with cystic areas and necrosis. Microscopically they are composed of monotonous sheets of small cells with round, oval or irregular nuclei. The nuclear-cytoplasmic ratio is high with nuclei that appear either hyperchromatic or clear and vesicular. Multiple mitoses may be seen. Although in some cases recognizable patterns of differentiation may be seen (e.g. rosette formation) they are often absent. Electron microscopy can be used to classify these tumours further according to their ultrastructural features. Both classic neuroblastoma and the other pPNETs show signs of neuroendocrine differentiation including interdigitating cytoplasmic processes, infrequent cell:cell junctions, dense-core neuroendocrine granules, microtubules/filaments and dense chromatin along the nuclear margin. Classic neuroblastoma tends to secrete catecholamines into the bloodstream whereas non-neuroblastoma pPNETs do not.[10]

Advances in immunohistochemical analysis has allowed further classification of such visually undifferentiated tumours according to the markers expressed on the cell surface. Synaptophysin, glial fibrillary acidic protein (GFAP), neurofilament proteins (NFPs) S-100 protein and neurone-specific enolase (NSE) are usually expressed in PNETs. Gaffney *et al.* have reported that GFAP can be found on the surface of many PNETs and may be useful in differentiating these tumours from undifferentiated non-neurogenic tumours such as germinomas or malignant lymphomas.[3] More recently an analysis of 86 cases of PNET seen at the University of Pennsylvania carried out by Janss showed GFAP positivity in 60 per cent of cases with 42 per cent co-expressing GFAP and NFPs.[19] Only 19 per cent expressed NFPs alone. Ewing's sarcomas and peripheral PNETs also express the p30-32 MIC-2 gene product (CD99) in over 90 per cent of cases.[20] Being a specific marker for peripheral PNET and Ewing's sarcoma, it is not expressed in central PNETs and thus is one way of differentiating central PNETs from pPNETs.[21] The combination of staining for Beta-2 microglobulin in addition to MIC-2 has been shown to facilitate the differentiation of peripheral from central neuroectodermal tumours.[22]

The close relationship between peripheral PNETs, Ewing's sarcoma (ES) and Askin's tumour has been illustrated elegantly by Batsakis *et al.* by drawing together their common staining characteristics and the genetic abnormalities which differ from those seen in central PNETs.[23] The ES-pPNET group may show deletions of the short arm of chromosome 1 and frequently has amplification of the N-*myc* gene. In contrast cPNETs show changes of chromosome 17 and do not show amplification. The ES-pPNET group alone consistently shows a reciprocal chromosomal translocation t(11;22)(q24;12).[24]

Conclusions

We present a case of peripheral PNET arising in the CPA. This case is unusual because of the age of the patient at presentation. This case highlights the difficulties in securing the correct diagnosis of this rare type of tumour. Neither the history or examination, nor the MRI were typical of vestibular schwannoma (the commonest CP angle tumour). Immunohistochemical assessment was vital in securing the correct diagnosis and planning appropriate management. Initial histological assessment was misleading and led to extensive efforts to identify a primary source for what was thought to be a metastatic deposit. Possible diagnoses considered included a neuroendocrine/neuroepithelial tumour or a metastatic small cell lung tumour. CT scanning and nuclear medicine imaging did not show any pathology in the chest. Positive staining for both MIC-2 and Beta-2-microglobulin in the absence of staining for cytokeratin and epithelial membrane antigen (EMA) confirm the diagnosis of a peripheral primitive neuroectodermal tumour.

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