Peripheral primitive neuroectodermal tumors (PNET) are rare neoplasms composed of small, round cells of presumed neural crest origin. These tumors arise outside the central and sympathetic nervous systems and have been called peripheral neuroepithelioma, Askin’s tumor, medulloepithelioma, and peripheral or adult neuroblastoma.6,12,27,31,41 Peripheral PNETs may display histological appearance similar to Ewing’s sarcoma, neuroblastoma, rhabdomyosarcoma, or lymphoma; however, they have distinct clinical, ultrastructural,2,3,31,41 immunocytochemical,40 and cytogenetic42 profiles. Recent studies have indicated that these tumors represent the neural extreme of differentiation of a broad range of neuroectodermal tumors, with Ewing’s sarcoma the most primitive and undifferentiated.7,13 Peripheral PNETs occur more commonly in children, this unusual neoplasm should be considered in the differential diagnosis of peripheral nerve neoplasms in adults. Early diagnosis is desirable because of its aggressive nature and poor outcome.

The authors describe a malignant peripheral primitive neuroectodermal tumor (PNET) that originated in the median nerve in an elderly adult. After the diagnosis was made by biopsy, the patient underwent radical local resection with interpositional vein grafting of the brachial artery. The tumor had the typical appearance of a primitive neural tumor with small, round cells forming rosettes. It stained positively for both the Ewing’s sarcoma/peripheral PNET antigen (HBA-71) and neuron-specific enolase, confirming its neural origin. Ultrastructural examination revealed dense core granules and suggested neural differentiation of the neoplasm. Cytogenetic analysis suggested a chromosome (11;22) translocation typical of peripheral PNET. Early reports consisted of tumors arising solely in peripheral nerves, but recent reports have focused mainly on tumors arising in the soft tissues other than nerves. There are no other cases of true PNET of peripheral nerve in the modern literature that have been fully characterized by immunohistochemical, ultrastructural, and cytogenetic criteria. Although peripheral PNETs occur more commonly in children, this neoplasm should be considered in the differential diagnosis of peripheral nerve neoplasms in adults. Early diagnosis is desirable because of its aggressive nature and poor outcome.

**KEY WORDS** • primitive neuroectodermal tumor • peripheral nerve • chromosomal translocation • HBA-71 antigen
Case Report

This 80-year-old woman presented with a 3-year history of weakness in the right upper extremity and difficulty with fine motor movements of the right index finger.

Examination. Examination revealed a mass in the medial aspect of the upper right arm. Mechanical manipulation of this mass produced electric shocks extending into the middle three digits of her right hand. She underwent an extensive radiological survey to locate a potential primary neoplasm, but none was found. Open biopsy of the mass revealed a PNET, which was treated with radiation therapy 3 months after initial diagnosis. She presented to the M. D. Anderson Cancer Center 5 months later complaining of aching pain in the second digit and shocklike pain on manipulation of the medial right upper arm. Neurological examination revealed decreased sensation to all modalities in the first three digits of the right hand. A magnetic resonance image demonstrated a well-circumscribed, extraosseous mass in the medial aspect of the right upper arm in the location of the median nerve, with probable involvement of the brachial artery (Fig. 1). A second metastatic workup, including bone scan and computerized tomography of the chest, abdomen, and pelvis, revealed no other site of tumor.

Operation and Intraoperative Findings. The patient underwent radical local resection of the tumor with reconstruction of the brachial artery. The incision from the previous biopsy was opened and the heads of the biceps and triceps muscles were separated. Dissection around the tumor was accomplished without violating the boundaries of its capsule. A fusiform enlargement of the median nerve was noted, with involvement of an overlying vein and a cutaneous nerve branch; they were ligated and cut distant from the tumor (Fig. 2). The ulnar, musculocutaneous, and radial nerves were identified, dissected free of surrounding tissue, and electrically stimulated to confirm their identity. Bone and muscle tissue were not grossly involved by tumor. The tumor was freed circumferentially and the brachial artery was clamped and divided proximal and distal to the tumor. The median nerve was then transected, and the tumor and artery were removed en bloc (Fig. 1). Frozen sections revealed normal nerve margins without tumor infiltration at the proximal and distal ends. An autologous saphenous vein graft was then harvested and a primary anastomosis made at the cut ends of the brachial artery.

Postoperative Course. The patient was discharged after an uneventful hospital stay; she had an expected complete right median nerve palsy. Three weeks later she was admitted to another hospital with dyspnea. Physical examination revealed the presence of a new lung mass and pleural effusions, presumably malignant in nature. Further aggressive therapy was not instituted at the patient’s wish and she expired 1 month later. No autopsy was performed.

Pathological Examination

Light Microscopy. For light microscopic examination, surgically excised tissue was fixed in 10% buffered formalin, routinely processed, and embedded in paraffin. Sections cut at 4-mm thickness were stained with hematoxylin and eosin.

Immunohistochemical Analysis. The avidin-biotin-peroxidase complex (ABC) method was used for all immunohistochemical studies. Tissue sections 4-μm thick were prepared from formalin-fixed, paraffin-embedded tissue, which was deparaffinized and rehydrated. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in absolute methanol. Sections were incubated in a humid chamber for 1 hour with one of the following primary antibodies: mouse monoclonal antibodies to desmin (Dako Corp., Carpinteria, CA; 1:100), leukocyte common antigen (LCA) (Dako Corp.; 1:500), HBA-71

![Fig. 1. Composite photomontage showing concordance in the radiographic and gross anatomical appearance of a primitive neuroectodermal tumor. Magnetic resonance image, T1-weighted, after injection of gadolinium in the upper right arm of the patient demonstrating the tumor’s extraosseous, medial location in the vicinity of the median nerve. Inset: Gross anatomical specimen after en bloc removal of the tumor and artery. The attached segment of brachial artery can be seen in the lower right portion of the specimen.](image1)

![Fig. 2. Intraoperative photograph depicting the anatomical relationships of a primitive neuroectodermal tumor to adjacent vessels and nerves. The hook lifts up a superficial cutaneous nerve stuck to the tumor surface. Inferior to the tumor lies first the brachial artery and immediately below the artery lies the ulnar nerve. The triceps muscle is seen in the lower half of the field. The tumor arising from the median nerve has been dissected free of surrounding tissues and vessel loops passed around that nerve proximal and distal to the tumor.](image2)
(Signet Laboratories, Dedham, MA; 1:100), chromo-
granin A (Boehringer-Mannheim, Indianapolis, IN;
1:300), and neurofilament proteins (NFP) (70-kD and
200-kD, Dako Corp.; 1:300), and polyclonal rabbit anti-
bodies to neuron-specific enolase (NSE) (Dako Corp.;
1:1000), and synaptophysin (Dako Corp.; 1:300). Avidin-
biotin-peroxidase Elite kits (Vector Laboratories, Burlin-
game, CA) were used for immunostaining, with 3-amino-
9-ethylcarbazole serving as the chromogen. Slides were
counterstained with Mayer’s hematoxylin. Antibody spec-
ificity was evaluated with known positive and negative
tissue controls.

Electron Microscopy. For ultrastructural examination,
small tissue fragments (approximately 1 mm³) were fixed
in buffered 2.5% glutaraldehyde, postfixed in 4% osmium
tetroxide, dehydrated through a graded ethanol series, and
embedded in Epon resin. Semithin (1-μm) sections were
stained with toluidine blue. Thin sections were stained
with uranyl acetate and lead citrate and examined by
transmission electron microscopy.

Results of Pathological Examination. Tissue sections
showed a malignant small-cell neoplasm with extensive
areas of necrosis (Fig. 3A). The tumor was located pri-
marily within the epineurium where it separated and dis-
placed nerve fascicles. Invasion through the epineurium
into surrounding connective tissue was present, as was
vascular invasion (Fig. 3B–D). Immunostaining revealed
the neoplastic cells to be strongly positive for HBA-71
(Ewing’s sarcoma/peripheral PNET antigen) and negative
for LCA, desmin, chromogranin, synaptophysin, and NFP
(Fig. 3B–D). Weak focal immunoreactivity for NSE was
present. By ultrastructural examination, neoplastic cells
exhibited irregular nuclear membrane profiles with promi-
nent heterochromatin and nucleoli. Cytoplasmic contents

Fig. 3. Photomicrographs and electron micrograph of
peripheral primitive neuroectodermal tumor. The neo-
plasm is a malignant small round-cell tumor (A) that
shows invasive spread through the perineurium into sur-
rounding skeletal muscle (B) as well as vascular invasion
(C). Strong immunopositivity for the Ewing’s sarco-
ma/peripheral primitive neuroectodermal tumor antigen,
HBA-71, is evident (D). Determination of the extent of
both local infiltration and vascular invasion is greatly
facilitated by immunostaining with HBA-71. By ultra-
structural examination (E), tumor cells exhibit irregular
nuclear membrane profiles, variably sized pools of glyco-
gen (labeled G), and clusters of polymorphic dense core
neurosecretory-type granules (arrow). A: H & E, × 400;
B and D: Immunoperoxidase for HBA-71, × 400; C:
Immunoperoxidase for HBA-71, × 100; E: Uranyl acetate/lead citrate, bar = 1 μm.

J. Neurosurg. / Volume 85 / July, 1996

165
included moderate numbers of mitochondria, abundant polysomes, variably sized glycogen deposits, and scattered clusters of dense core granules. Occasional poorly formed desmosome-like intercellular junctions were also identified (Fig. 3E).

Cytogenetic Analysis. Fluorescence in situ hybridization (FISH) was performed on acetic acid/methanol–treated chromosome spreads obtained from primary culture of the tumor specimen. The probe was generated from B45C11 yeast artificial chromosome (YAC) B45C11. The FLII locus on a normal chromosome 11 and a larger, derivative chromosome 11 (left) (showing a short fragment of chromosome 22 distal to the FLII locus) are identified by the arrows. These orange bands, faintly shown here, are more prominently seen on the analogous color photographs (not shown).

In the FISH preparation two distinct signals were observed in the majority (> 80%) of metaphase spreads from a primary in vitro culture of the tumor (Fig. 4). One signal mapped to the telomeric region of the long arm of normal chromosome 11, with a fractional telomeric length (FTL) of 0.97 ± 0.04, which is the reported position of the FLII gene. A second signal mapped to a derivative extended chromosome 11 with a FTL of 0.85 ± 0.06. The FTLs were similar to those previously reported for the translocation of a FLII gene fragment from chromosome 11 onto chromosome 22. A signal was not observed for the putative translocated fragment of FLII on a derivative chromosome 22, as previously observed by Selleri, et al., using B45C11 hybridization on tumor specimens exhibiting the t(11;22)(q24;q12) translocation. These results, however, do suggest a rearrangement of the genomic region that includes the FLII locus in this tumor.

Discussion

We present the clinical, operative, and pathological findings observed in the case of a PNET involving the median nerve in an adult. Detection of the mass was preceded by neurological symptoms referable to the median nerve, the site of origin. Two complete radiological surveys failed to reveal a primary tumor that could be the source of a metastasis. The tumor was treated with radiation therapy prior to definitive surgery. Radical surgical resection of the tumor and involved brachial artery and subsequent vascular reconstruction was performed without incident. However, the patient died a short time later with presumed lung metastasis from the tumor.

Historical Aspects

Stout is generally given credit for reporting the first well-documented peripheral PNET in 1918. That tumor arose from the ulnar nerve in a 42-year-old man and was composed of small, round cells that formed rosettes. A poorly documented case of a similar tumor reported in 1892 by Garre was accepted by Stout as fitting the historical criteria for this tumor and may represent the original report of this neoplasm. From 1918 to 1968, eight more cases of PNET involving peripheral nerves were reported. All of these tumors occurred in a variety of nerves in the extremities in adult patients, the youngest of whom was 35 years old. The term “neuroepithelioma” was coined by Stout and Murray when describing a PNET of the radial nerve in a 35-year-old man. The patient reported here is the oldest individual yet described with a peripheral nerve PNET.

In 1969, Lagerkvist, et al., were the first to report this tumor in a peripheral nerve of a child. In reporting a case of PNET arising from the sciatic nerve in a 6-year-old, Nesbitt and Vidone not only confirmed its occurrence in children but also emphasized, in addition to its characteristic histological appearance, its distinct localization within the nerve sheath and the lack of evidence for metastatic neuroblastoma (by autopsy) necessary for the diagnosis of this tumor. Since their report, sporadic cases have reaffirmed the occurrence of PNET in peripheral nerves of adults and children. However, recent large series reviewing the clinicopathological characteristics of soft-tissue peripheral PNETs have demonstrated few, if any, definitely arising from peripheral nerves. This finding has resulted in a shift of the attention of pathologists to the soft-tissue form not definitely associated with peripheral nerves.

Review of the literature reveals a paucity of cases of peripheral PNET arising from peripheral nerves (Table 1). Including the initial report of Garre, 14 cases arising from peripheral nerves were published prior to the case of Nesbitt and Vidone in 1976, and 20 cases have been reported since then. Abell, et al., reported a case arising from an intercostal nerve, but this was incompletely documented, and hence, it cannot be ascertained with certainty if this neoplasm arose from within the nerve proper or if it should be more appropriately called an Askin’s tumor.
of the chest wall. There have been only two previously reported PNETs arising from the median nerve,\textsuperscript{5,25} as the majority of those in the upper extremity arise from the radial or ulnar nerves. Primitive neuroectodermal tumors have also been reported in nerves within the orbit\textsuperscript{35,43} and cauda equina\textsuperscript{20,24} and from a cranial nerve.\textsuperscript{26} Although the data are incomplete and few conclusions can be drawn, these reports show that the average age of patients with peripheral nerve PNET at diagnosis is 28.2
\textsuperscript{3.4} years (mean \textsuperscript{standard error of the mean}) with a mean survival of 11.6
\textsuperscript{1.4} months. The individual reported here was much older than others with this neoplasm, and she survived for a shorter time than expected.

Pathological Appearance

The histological appearance of this tumor was that of a classic peripheral nerve PNET composed of small, round cells. Rosettes were not a feature in this case. Although the neoplastic cells invaded the adjacent connective and vascular tissue, they were located predominantly within the epineurium of the median nerve. This tumor’s spectrum of NSE and HBA-71 immunoreactivity, as well as its negative immunoreactivity for LCA and desmin, place it firmly in the peripheral PNET category and distinguish it from neuroblastoma, lymphoma, and rhabdomyosarcoma. Additional evidence for its origin within the nerve from a primitive neural precursor comes from the ultrastructural findings of dense core granules and the lack of a definite source of a primary neoplasm, such as a neuroblastoma. The presence of a chromosomal translocation commonly seen in peripheral PNETs strengthens the diagnosis made here of a tumor of neural origin.

Few of the 35 peripheral nerve PNETs previously described are as completely documented with respect to ultrastructural and immunohistochemical criteria as the present case. Dense core neurosecretory granules implying origin from the neural crest have been shown in the 10 cases examined by electron microscopy in the literature\textsuperscript{3,16,22,23,27,41} and also in a cell line established from a peripheral nerve PNET.\textsuperscript{15} Immunohistochemical demonstration of antigens suggestive of a neural origin was performed on only eight of the cases of peripheral nerve PNET in the literature.\textsuperscript{12,16,22,23} This analysis showed NSE staining in seven (87%) but no staining with synaptophysin. Llombart-Bosch, \textit{et al.},\textsuperscript{22} and Marina, \textit{et al.},\textsuperscript{23} subjected their tumors to a comprehensive panel of specific antibodies, but their cases make up only four of the 35 peripheral nerve cases. Only six other cases of peripheral

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Author & Year} & \textbf{Total No. of Cases*} & \textbf{Cases of Peripheral Nerve PNETs} & \textbf{Nerve of Origin} & \textbf{Patient Age (yrs)} & \textbf{Survival (mos)} \\
\hline
Garrè, 1892 & 1 & 1 & sciatic & 31 & 6.5 \\
Stout, 1918 & 1 & 1 & ulnar & 42 & 3 \\
Cohn, 1928 & 3 & 1 & median & 35 & \ \\
 & & 1 & radial & 53 & 9 \\
 & & 1 & spinal accessory & 53 & \ \\
Hackel, 1934 & 1 & 1 & radial & 37 & \ \\
Stout & Murray, 1942 & 1 & 1 & radial & 35 & \ \\
Stout, 1949 & 1 & 1 & sciatic & 47 & \ \\
Schmincke, 1956 & 1 & 1 & radial & 47 & \ \\
Harkin & Reed, 1969 & 1 & 1 & radial & \ \\
Lagerkvist, \textit{et al.}, 1969 & 3 & 1 & brachial plexus & 1.25 & 14 \\
 & & 1 & radial & 7.5 & \ \\
 & & 1 & T-9 & 0.4 & 3.75 \\
Mennel & Zülch, 1971 & 1 & 1 & median & 52 & \ \\
Nesbitt & Vidone, 1976 & 1 & 1 & sciatic & 6 & 24 \\
Ishikawa, \textit{et al.}, 1979 & 1 & 1 & C-8 root & 28 & 8 \\
Bolen & Thornig, 1980 & 1 & 1 & S-1 root & 22 & \ \\
Harper, \textit{et al.}, 1981 & 2 & 1 & lat popliteal & 29 & 6 \\
 & & 1 & ulnar & 45 & \ \\
Nakamura, \textit{et al.}, 1982 & 1 & 1 & sciatic & 0.5 & \ \\
Samuel, 1982 & 1 & 1 & ulnar & 59 & \ \\
Hashimoto, \textit{et al.}, 1983 & 15 & 1 & sciatic & \ \\
 & & 1 & ulnar & \ \\
Voss, \textit{et al.}, 1984 & 1 & 1 & musculocutaneous & 0.25 & 14 \\
Jürgens, \textit{et al.}, 1988 & 20 & 3 & lumbar & 3 & \ \\
 & & 1 & brachial plexus & \ \\
 & & 1 & ulnar & \ \\
Llombart-Bosch, \textit{et al.}, 1989 & 10 & 1 & sciatic & 38 & 3 \\
Marina, \textit{et al.}, 1989 & 26 & 1 & sciatic & 23 & 18.8 \\
 & & 1 & leg† & 18 & 24.7 \\
 & & 1 & pelvic wall† & 13 & 15.7 \\
current report, 1996 & 1 & 1 & median & 80 & 9 \\
\textbf{total} & \textbf{93} & \textbf{36} & \ \\
\hline
\end{tabular}
\caption{Previous reports of documented peripheral PNET arising from peripheral nerves}
\end{table

* Total number of cases of peripheral primitive neuroectodermal tumor (PNET) (including extraneural sites) presented in report.
† Exact nerve of origin not specified, but the tumor was reported to arise from a major nerve branch in this region.

\textit{J. Neurosurg.} / Volume 85 / July, 1996

167
nerve PNET have been analyzed both ultrastructurally and immunohistochemically.\textsuperscript{16,22,23}

**Cytogenetic Analysis**

Although the cytogenetics of peripheral extraneural PNET have been extensively studied,\textsuperscript{42} such analyses have not been performed on previously reported cases of PNET of peripheral nerves. The abnormality typically seen is t(11;22)(q24;q12), that is, translocation of a small fragment of chromosome 22 onto the disrupted telomeric region of chromosome 11, with the linkage occurring at a breakpoint within the FLI1 gene locus.\textsuperscript{33} This translocation produces an elongated, derivative chromosome 11 and a truncated, derivative chromosome 22, each of which carries a portion of this gene. As the remaining normal chromosome 11 also carries the gene, three hybridization signals are expected in FISH using a comprehensive and specific DNA probe. In the present case, the derivative chromosome 22 was not demonstrated, although the others were shown at cytogenetic locations previously reported by others.\textsuperscript{34} However, our hybridization procedure utilized Alu- and L1-generated PCR probes derived from the YAC, rather than isolated YAC DNA; these shorter oligonucleotides incompletely reproduce the YAC (particularly because the YAC is Alu-poor) and thus explain the absence of a detectable derivative chromosome 22. Despite this partial reproduction of the expected cytogenetic findings, the presence of a derivative chromosome 11, with hybridization signal at a site previously recorded for t(11;22)(q24;q12), by itself strongly suggests that the pathognomonic translocation was present in this tumor.

**Conclusions**

This case of primary malignant peripheral PNET arising in a peripheral nerve of an adult has many similarities to other cases reported during the early history of this neoplasm, but as knowledge of the scope of this tumor has increased in recent years, cases involving peripheral nerves in adults are less frequently encountered. It is still important to consider PNET in the differential diagnosis of peripheral nerve neoplasms in both adults and children and to remember the natural history and poor outcome of these tumors, which argue for early radical excision and against biopsy and radiotherapy alone.

**References**


Median nerve PNET


Manuscript received November 16, 1995.
Accepted in final form February 6, 1996.

Address reprint requests to: Ian E. McCutcheon, M.D., Department of Neurosurgery, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 64, Houston, Texas 77030.