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Malignant peripheral neuroectodermal tumours of childhood and adolescence*

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Summary. Seventeen cases of malignant peripheral neuroectodermal tumour (MPNT) were studied by means of light microscopy, immunohistochemistry and electron microscopy. There were nine males and eight females. The mean age of the 17 patients was 10 years with a range of seven months to 20 years. The vast majority of tumours was located in the trunk. Histologically, they closely resembled Ewing's sarcoma, although minor differences were obvious. Special findings included ganglion cells and Flexner rosettes. In 10/11 cases positive staining for neuron-specific enolase (NSE) was obtained. Five of 10 tumours were positive for protein S-100. Three contained vimentin, two neurofilaments and one vimentin, neurofilaments and GFAP. Neurosecretory granules were noted in the three cases studied. Five patients died, three are alive with disease and five patients are alive without evidence of disease. It is concluded that these tumours form a homogeneous group, although the grade of differentiation varies. The prognosis in most cases is poor. Distinction from Ewing's sarcoma is possible by staining for NSE and by electron microscopy.

Key words: Neuroepithelioma – Histology – Immunohistochemistry – Neuron-specific enolase – Ultrastructure

Introduction

Malignant tumours of peripheral nerves include malignant schwannoma and its variants, neuroepithelioma (malignant peripheral neuroectodermal tumour; MPNT), olfactory neuroepithelioma and extraspinal ependymoma. Neuroepithelioma may occur at any age, but is rarely encountered during childhood and adolescence (Enzinger and Weiss 1983). The retroperitoneum,

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mediastinum, pelvis, extremities, trunk and neck are the most common locations (Hajdu 1979). Although most cases have been reported to occur in association with major peripheral nerves, this anatomical relationship is not always evident (Hashimoto et al. 1983). Histologically, neuroepithelioma may present various histological appearances (for review see Harper et al. 1981). Some tumours may show differentiation into Homer-Wright rosettes and/or Flexner rosettes. However, other cases may lack these diagnostic features, and confusion with other small-, round-cell tumours may occur (Enzinger and Weiss 1983). Homer-Wright rosettes have also been described in the so-called small cell tumour of the thoracopulmonary region ("Askin tumour"). The histogenetic relationship of this type of tumour to neuroepithelioma is as yet unknown (Askin, personal communication). A neuroectodermal nature has been suspected in the original article on the basis of ultrastructural findings (Askin et al. 1979) and appears now to be substantiated by positive reaction of the neoplastic cells for neuron-specific enolase (Linnoila et al. 1983; Triche and Askin 1983; Gonzalez-Crussi et al. 1984; Tsokos et al. 1984).

The neoplasm most closely resembling "Askin tumor" is Ewing's sarcoma. Recently, we saw four small-, round-, blue-cell tumours which were located in the chest wall and had initially been diagnosed as "consistent" with Ewing's sarcoma. We did not find any rosettes in these tumours despite extensive search. When they were re-examined immunohistochemically for the presence of neuron-specific enolase (NSE), it became evident that a diagnosis of Ewing's sarcoma could no longer be sustained. Stimulated by these observations and data recently reported in the literature we performed a retrospective analysis on all cases of small-, round-, blue-cell tumours located in the chest wall, which had been diagnosed initially as Ewing's sarcoma and "Askin tumour". In addition, we reinvestigated all cases of MPNT which were located elsewhere.

Material and methods

Seventeen cases with the initial diagnosis of Ewing's sarcoma located in the chest wall, seven cases of "Askin tumour" and six cases of MPNT from the files of the Pediatric Registry in Kiel form the basis of this study.

Paraffin sections stained with haematoxylin and eosin (H & E), Giemsa, periodic acid-Schiff (PAS), reticulin stain (Bielschowsky) and Goldner stain were available in all cases. For immunohistochemical demonstration of NSE and protein S-100, paraffin sections were recut in 16 cases including nine cases of Ewing's sarcoma, four cases of "Askin tumour" and three cases of MPNT. In six cases of MPNT tissue had been fixed in alcohol for investigation of intermediate filaments. This study was performed by Dr. M. Altmannsberger (Göttingen) as previously described (Altmannsberger et al. 1981).

Neuron-specific enolase and protein S-100 were demonstrated by means of the peroxidase-antiperoxidase (PAP) method according to Sternberger et al. (1970). Briefly, sections were dewaxed in xylene, rehydrated in alcohol and incubated with the specific antibody, followed by incubation with swine anti-rabbit Ig as linking antibody. The PAP complex (Dakopatts, Hamburg, FRG) was applied in the third step. Primary antibodies against NSE and protein S-100 (Dakopatts, Hamburg, FRG) were used in concentrations of 1:300 and 1:100, respectively. Negative controls were performed applying normal swine serum instead of the specific antibody.

Table 1. Clinical data of patients with malignant peripheral neuroectodermal tumour

No.	Age	Sex	Location	Treatment	Survival	Metastases
1	7 months	m	skull	Op, CTX, RT	6 years, NED	
2	9 months	f	chest wall	Op	4 weeks, died	
3	33 months	m	neck	Op, CTX, RT	17 months, died	bone, brain
4	4 years	m	chest wall	Op, CTX	6 weaks, died	lymph nodes, lungs
5	6 years	m	chest wall	Op, CTX	12 weaks, AWD	liver, bone, lungs
6	7 years	m	chest wall	Op, CTX, RT	3 years, NED	
7	7 years	f	chest wall	Op, CTX	unknown	
8	8 years	f	pelvis	Op, CTX	6 months, NED	
9	10 years	f	chest wall	Op, CTX, RT	2 years, NED	
10	13 years	f	chest wall	Op, CTX	8 months, died	bone
11	14 years	f	chest wall	unknown	unknown	
12	14 years	m	lower limb	unknown	unknown	
13	15 years	m	chest wall	unknown	unknown	
14	15 years	f	lower limb	Op, CTX	9 months, NED	
15	16 years	m	mediastinum	Op, CTX	9 months, died	lungs
16	17 years	m	lower limb	Op, CTX, RT	11 months, AWD	bone
17	20 years	f	chest wall	unknown	unknown	

CTX = Chemotherapy NED = No evidence of disease
RT = Radiotherapy AWD = Alive with disease

Electron microscopic examination was done in three cases. Fresh tissue was fixed in 2.5% buffered glutaraldehyde (0.1 M phosphate buffer, pH 7.4) for 2 h at 4° C, postfixed in 1% osmium tetroxide and dehydrated in a graded acetone series. The fixed tissue was then embedded into araldite. Thin sections stained with uranyl acetate and lead citrate were studied in a Siemens 101 electron microscope.

Results

Among the total number of 30 cases reviewed 17 revealed closely similar histological features. Some clinical data of these 17 patients are summarized in Table 1. One case will be reported in more detail to illustrate the aggressive clinical behavior of some of these tumours.

Case report

This 4-year-old boy was admitted to the hospital because of heavy left-sided chest pain of 2 months duration and fever of 39.2° C for 10 days.

On physical examination the boy was found to be in poor general condition. X-ray demonstrated a large opacity in the left hemithorax (Fig. 1). 750 ml of sanguineous fluid could be drained from the left pleural cavity. On cytological examination it revealed the presence of undifferentiated small round neoplastic cells. X-ray tomography demonstrated partial destruction of the sixth rib. No skeletal metastases were detected on bone scan. Bone marrow aspiration and lumbar puncture were also negative for tumour cells. Laboratory findings included normal levels for vanilmandelic acid

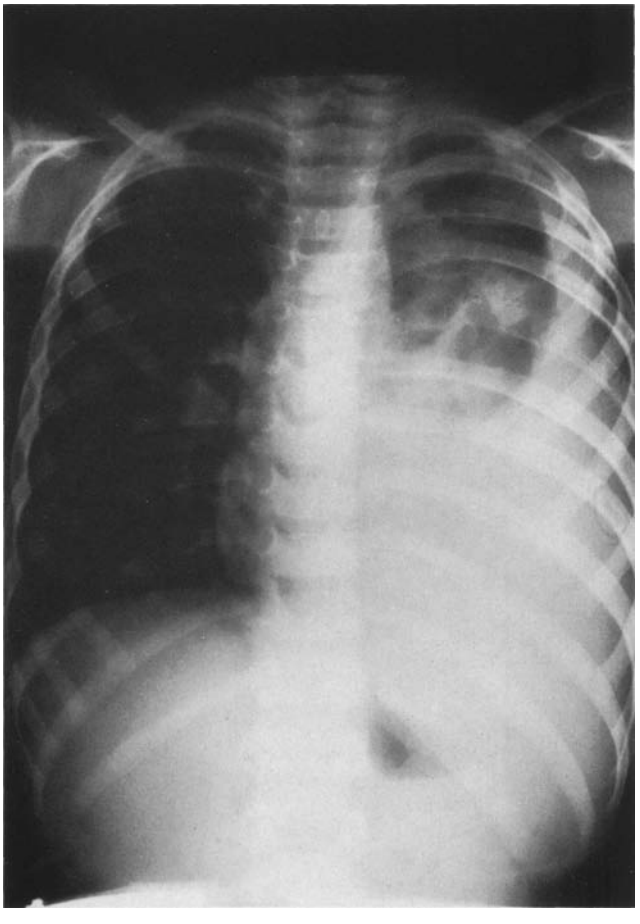

Fig. 1. Chest roentgenogram demonstrating a large mass in left hemithorax (4-year-old boy)

(VMA), homovanillic acid (HVA), and 3-methoxytyramine in 24 h urine. Excretion of metanephrine and normetanephrine was increased. Concentration of metanephrine was elevated, but normal for normetanephrine. At thoracotomy, a large tumour mass was found in the left hemithorax extending to the right of the vertebral column above the fifth rib, into the neural foramen and down below the diaphragm. Multiple enlarged lymph nodes were present along the oesophageal portion of the tumour mass and in the oesophageal hiatus. The sixth rib, the intrathoracic and retroperitoneal portions of the mass and the paraoesophageal lymph nodes were resected. Portions of the mass close to the vertebral column and multiple enlarged abdominal lymph nodes had to be left in place. Five days after operation the patient developed paraplegia of both lower extremities. Laminectomy extending from Th 3 to Th 9 was performed and the epidural tumour was completely resected. Postoperatively, chemotherapy with methylprednisolone, vincristine, hydroxyurea, procarbazine, CCNU, cis-platinum, cytoxin

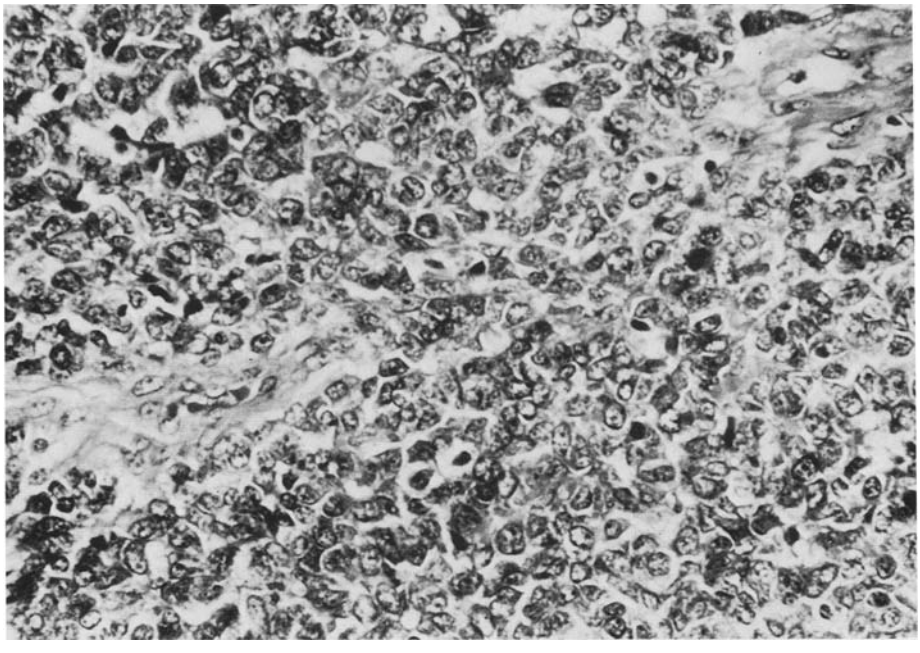

Fig. 2. Malignant peripheral neuroectodermal tumour (KT-No. 183/84). The tumour consists of small to medium-sized cells with round-to-oval nuclei and indistinct cytoplasm (HE, × 350)

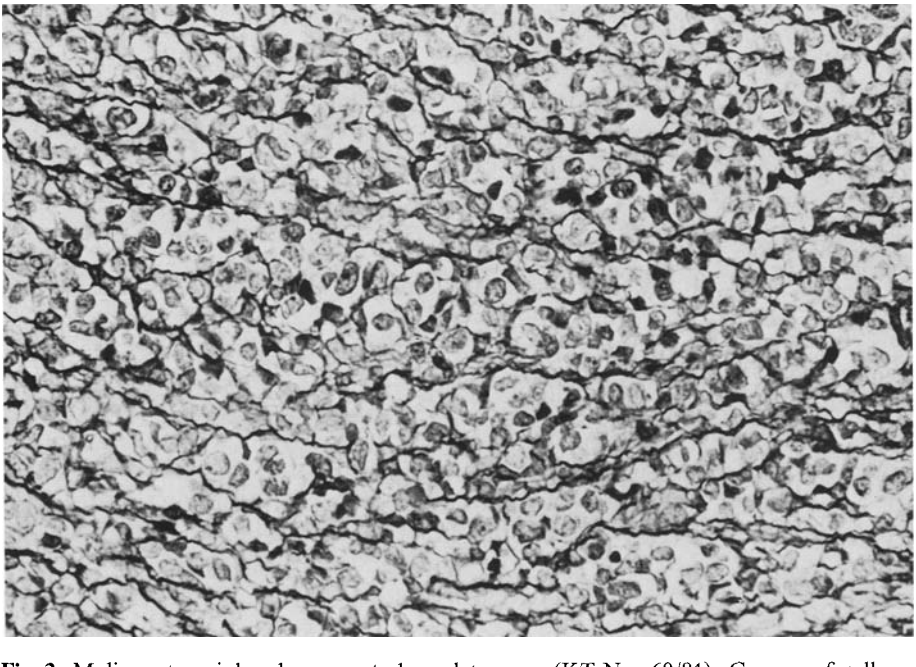

Fig. 3. Malignant peripheral neuroectodermal tumour (KT-No. 60/81). Groups of cells are surrounded by reticulin fibrils (Ag, × 350)

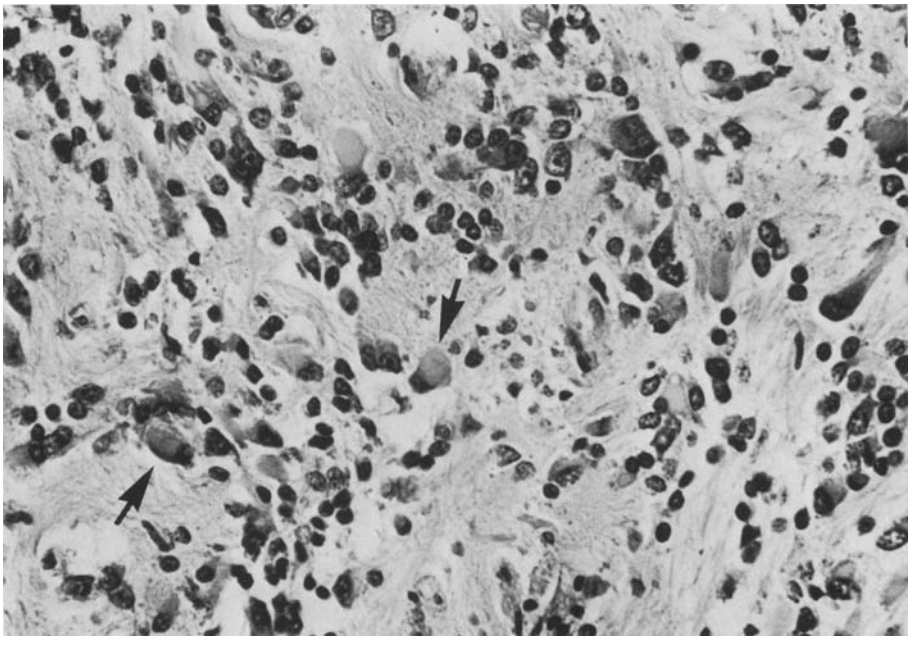

Fig. 4. Malignant peripheral neuroectodermal tumour (KT-No. 657/83). Portion of tumour demonstrating immature ganglion cells (arrows) and neurofibrillary structures. Staining for GFAP was negative (HE, ×350)

arabinoside and cyclophosphamide was instituted. Despite this aggressive protocol the paravertebral tumour portion increased in size and a metastasis was noted in the right lung. Treatment with methotrexate was now begun, but again no reduction of tumour size was achieved. The patient died 6 weeks after admission. No autopsy was done.

Histological findings

Except for one tumour which was located subcutaneously all infiltrated deep soft tissue structures. In addition, tumour tissue in one case invaded the outer layers of the tibial cortex. All lesions were highly cellular consisting of small to medium-sized, tightly packed cells with poorly developed cytoplasm and ill-defined cytoplasmic borders. Nuclei were usually round-to-oval and contained clumped, but evenly distributed chromatin and up to three minute nucleoli (Fig. 2). In two tumours the nucleoli were prominent and stained amphophilic on H & E stain. Generally, mitotic activity was moderate, although in two cases there were numerous mitotic figures (up to 30 mitoses/10 HPF).

In some tumours, the neoplastic cells were arranged in a pseudoalveolar or lobular pattern. Blood vessels were always surrounded by reticulin fibrils which also extended to some degree between adjacent tumour cells. Cell complexes were usually devoid of reticulin fibrils. In only two tumours

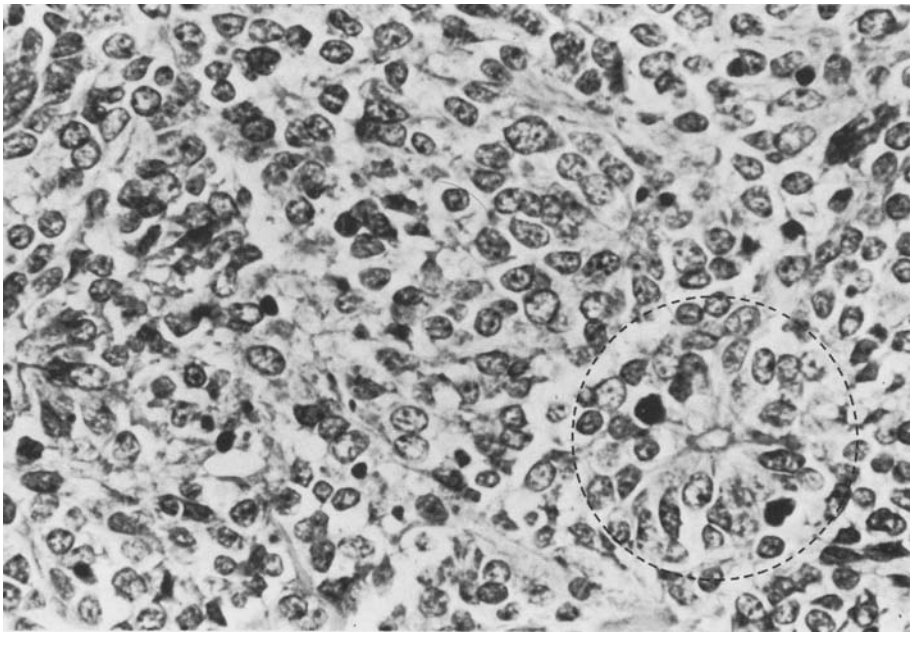

Fig. 5. Malignant peripheral neuroectodermal tumour (KT-No. 243/81). Cells are arranged in Flexner rosette (right lower corner; HE, ×350)

groups of cells were surrounded by reticulin fibrils (Fig. 3). PAS-reaction was positive in 10 of the 17 cases (1 case: +++, 6 cases: ++, 3 cases: +), whereas seven were PAS-negative. Two tumours revealed small areas with ganglion cells of various stages of differentiation and neurofibrillary structures (Fig. 4). Flexner-type rosettes and tubular structures were found in another case (Figs. 5, 6). Pseudorosettes around capillary blood vessels were present in many tumours. One showed areas of necrosis with calcification. Reactive bone formation was identified in only three cases.

Ultrastructural findings

Polygonal neoplastic cells were closely apposed posessing round-to-oval nuclei with finely clumped chromatin and small nucleoli. In places, they had cytoplasmic extensions of varying width, occasionally wrapping around other cells. Tumour cells and/or cytoplasmic processes were connected by small desmosome-like junctions. A significant finding in all cases was the presence of a small number of dense-core neurosecretory granules which often occurred in groups of two or three (Fig. 7). Other findings included some microfilaments, a moderate number of mitochondria and many polyribosomes. There were also some short cisternae of rough endoplasmic reticulum. The Golgi complex was inconspicous. Fibrin was occasionally seen in the extracellular space.

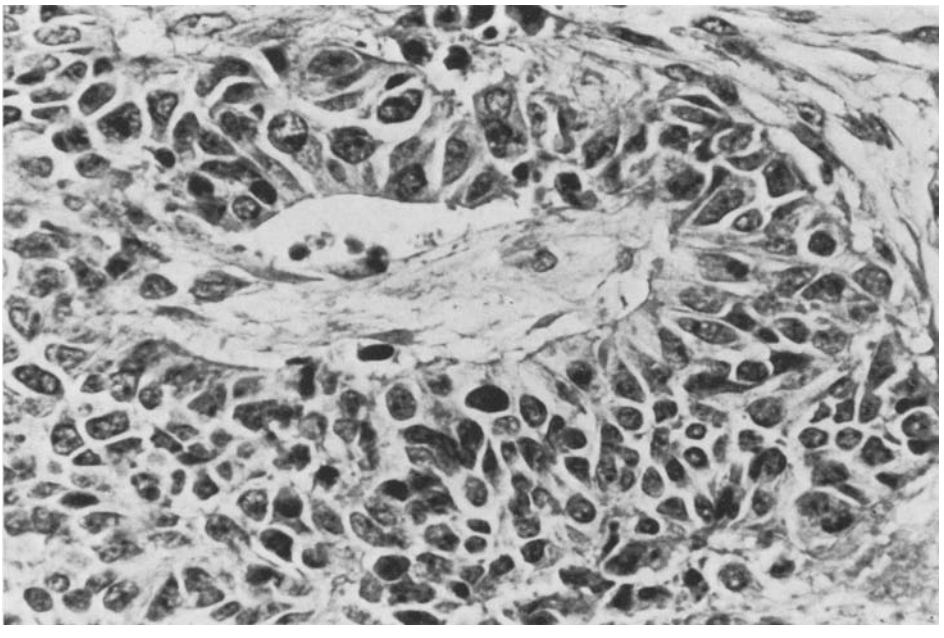

Fig. 6. Malignant peripheral neuroectodermal tumour (KT-No. 243/81). Tumour cells form tubular structure (HE, × 560)

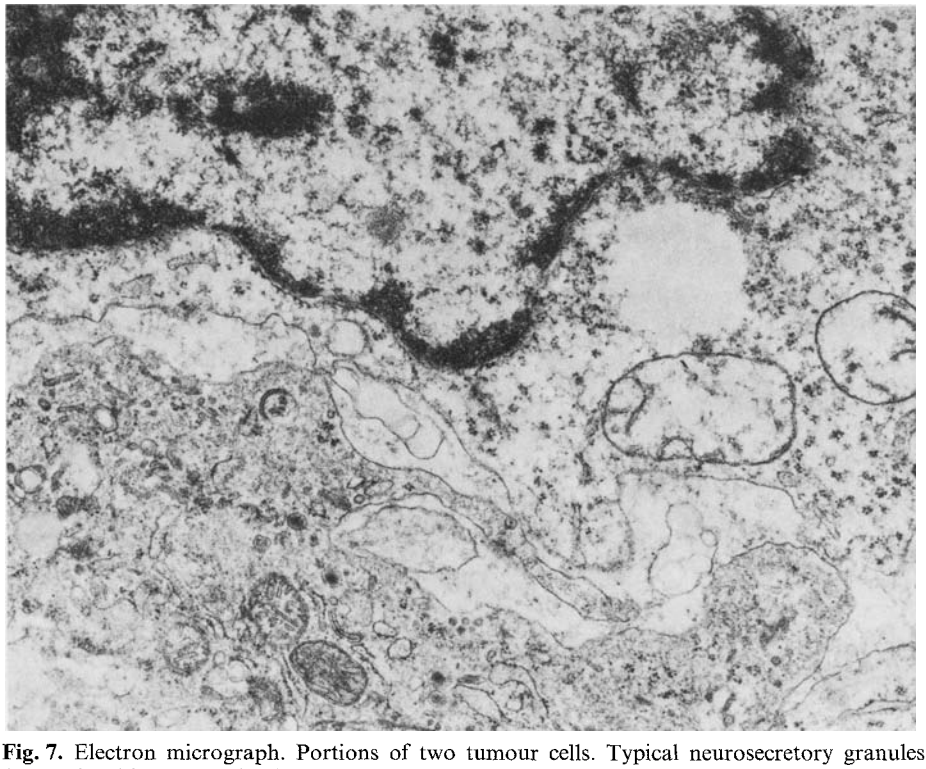

Fig. 7. Electron micrograph. Portions of two tumour cells. Typical neurosecretory granules (arrow heads) are seen in the cytoplasm of one of the two (Uranyl acetate and lead citrate, × 16,500)

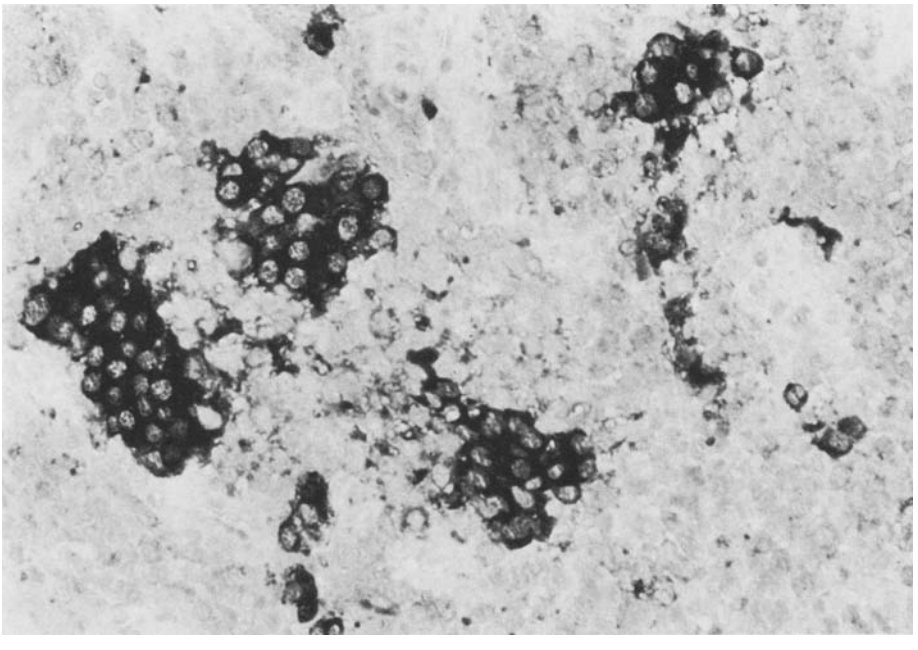

Fig. 8. Malignant peripheral neuroectodermal tumour (KT-No. 52/81). Groups of cells are positive for neuron-specific enolase (PAP, ×350)

Table 2. Type of intermediate filament present in malignant peripheral neuroectodermal tumour

Type of filament	*n*
Vimentin	3/6
Neurofilaments	2/6
Vimentin, Neurofil. and GFAP	1/6

Immunohistochemical findings

Ten of 11 tumours studied by immunohistochemical methods revealed cells with positive staining for NSE. The number of positive cells, however, varied considerably from tumour to tumour and even from area to area in the same specimen. Only cells with a darkly brown-staining cytoplasm in well preserved areas were considered positive (Fig. 8).

In five cases cells reacted positively for protein S-100. In two of these strongly positive cells with long cytoplasmic processes were noted in the stromal portion.

The type of intermediate filaments in the tumour cells varied (Table 2). Vimentin was found in three cases, neurofilaments in two other cases and one tumour expressed vimentin, neurofilaments and glial fibrillary acid protein (GFAP; Fig. 9). On conventional light microscopy this tumour demonstrated Flexner rosettes and tubular structures.

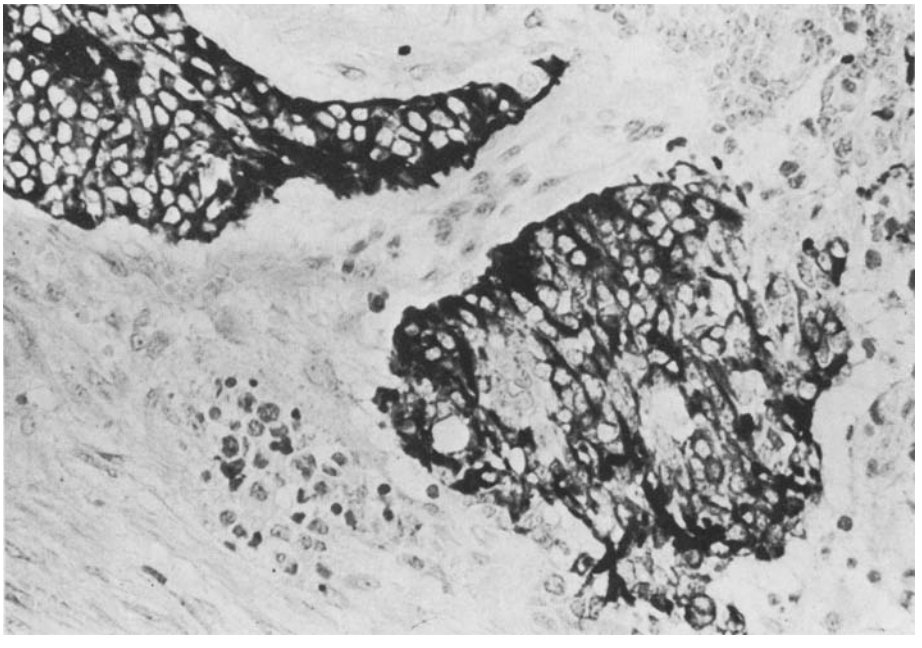

Fig. 9. Malignant peripheral neuroectodermal tumour (KT-No. 243/81). Most cells stain positively for glial fibrillary acid protein (PAP, ×350)

Discussion

Primitive neuroectodermal tumours are usually encountered in the central or in the peripheral nervous system. From the present investigation and in previous studies it has become evident that in some instances this type of tumour may also arise in soft tissue, lacking any relationship to peripheral nerves.

Peripheral neuroepithelioma is rare. Hajdu (1979) identified 31 cases of peripheral neuroepithelioma among a total number of 2489 (1.1%) soft tissue sarcomas. Recently, Enjoji and Hashimoto (1984) made a survey of 8 cases (1.1%) of malignant neuroepithelioma among 752 cases of soft tissue sarcoma. At the Pediatric Tumour Registry in Kiel we have collected 17 cases among 271 malignant soft tissue tumours (6.3%). These 17 cases also include so-called "Askin tumours". Among our cases there are also tumours which did not reveal rosettes, but expressed the neural marker NSE or were otherwise histologically indistinguishable.

According to Enzinger and Weiss (1983) neuroepithelioma may occur at any age, although most patients are more than 20 years old. Hajdu (1979) does not specifically mention the age distribution of his cases, although he states that these tumours occur in young adults or adults. The median age of the 15 patients reported by Hashimoto et al. (1983) was 21 years with a range from 2 to 43 years. Only three patients were younger than 15 years. In the present study the patient's age ranged from seven

months to 20 years with a mean age of 10 years. Twelve patients were 15 years of age or younger. The particular age distribution in our material is most likely due to the selection of tumours from the Pediatric Tumour Registry. Although the age distribution in our material is not representative, it demonstrates again that these lesions may occur in very young patients.

Very few data are available on the sex distribution in MPNT. There were 18 males and 13 females in Hajdu's study (1979), and a clear female predominance (2:1) was noted by Hashimoto et al. (1983). In our own patients the sex distribution was about equal. Interestingly, 75% of the "malignant small cell tumours of the thoracopulmonary region in childhood" occur in female patients (Askin et al. 1979).

No dominant location for MPNT has been reported in the literature. Most tumours in the study of Hajdu (1979) arose in the retroperitoneum, followed in frequency by mediastinum and pelvis. Only three of the 31 tumours were found on the trunk, whereas the trunk was the second most frequent location of MPNT's reported by Hashimoto et al. (1983). It was the most common affected site in the present study (66%).

The presence of glycogen in more than half of our cases was one of the most significant histological findings. This observation is in accordance with the notion that the presence or absence of glycogen can no longer be used as a discriminating feature in the differential diagnosis of small-, round-, blue-cell tumours. Glycogen was found not only in our cases, but was also present in two of 10 cases reported by Hashimoto et al. (1983) as well as in 10 of 15 cases described by Linnoila et al. (1983). Since glycogen is also seen in some neuroblastomas and in most cases of Ewing's sarcoma, the question arises: Are there any morphological criteria, which distinguish MPNT from the other small-, round-, blue-cell tumours, especially neuroblastoma and Ewing's sarcoma? In our opinion it is possible to make a distinction between these types of tumour in most cases. The various criteria and their expression in Ewing's sarcoma, neuroepithelioma and undifferentiated neuroblastoma are listed in Table 3. However, to confirm the diagnosis reached by conventional light microscopy, additional studies including immunohistochemistry and electron microscopy should be performed whenever possible. The most useful and least time consuming technique is immunohistochemical staining for NSE. Hashimoto et al. (1983) found this enzyme in six of eight cases of neuroepithelioma and Linnoila et al. (1983) demonstrated it in all cases of "Askin tumour". In this study we were able to show NSE-positivity in all but one of our cases of neuroepithelioma. Negative staining, however, should not rule out a diagnosis of MPNT, if the histological criteria are adequately demonstrated. This assumption is based on the fact that various factors, including time lapse until fixation, duration of fixation and embedding process can cause negative staining (Hashimoto et al. 1983). Therefore, immunostaining for NSE is a useful method only if it is done in a methodologically correct manner and interpreted critically (Dranoff and Bigner 1984, Vinores et al. 1984).

While the immunostaining procedure for NSE can be done in every case in which paraffin blocks are available, electron microscopic study is

Table 3. Histological, immunohistochemical and ultrastructural features serving to distinguish neuroepithelioma (malignant peripheral neuroectodermal tumour) from Ewing's sarcoma and undifferentiated neuroblastoma

	Ewing's Sarcoma	Neuroepithelioma	Neuroblastoma, undiff.
Fibrovascular septae	rare	few	frequent
Foci of calcification	rare	rare	frequent
Pseudorosettes	rare (degenerative)	occasional	in >50%
Nuclei	round (ground glass appearance)	round, moderately polymorphic, finely clumped chromatin	polymorphic and hyperchromatic
Nucleoli	small	small	barely recognizable
PAS-reaction	mostly positive	variable	mostly negative
Reticulin fibrils	none	very few	few
Neuron-specific enolase	negative	positive	positive
Protein S-100	negative	sometimes positive	negative
Vimentin	positive	sometimes positive	negative
Neurofilaments	negative	sometimes positive	negative
GFAP	negative	rarely positive	negative
Neurosecretory granules	absent	few	variable

usually restricted to a few selected cases. In these cases, however, it proved to be diagnostic, since neurosecretory granules were demonstrated (Askin et al. 1979; Bolen and Thorning 1980, Gonzalez-Crussi et al. 1984). We found neurosecretory granules in all three cases.

Although the neoplastic cells contain neurosecretory granules, urinary vanilmandelic acid excretion is not increased above normal levels (Seemayer et al. 1975; Enzinger and Weiss 1983; Hashimoto et al. 1983). Such a discrepancy is also known to occur in some cases of undifferentiated neuroblastoma and has been attributed to the immaturity of the neoplastic cells (Romansky et al. 1976). The tumour cells may store catecholamines, but are unable to secrete them into the blood stream. The absence of elevated VMA excretion was one of the criteria for inclusion of a case in the present study.

Because of the small number of cases reported in the literature and the different therapeutic modalities employed, no definite conclusions can be drawn concerning the biological behavior of peripheral neuroepithelioma, especially in childhood and adolescence. Three of four patients in the series of Seemayer et al. (1975) died within 6 months, 2 years and $5^1/_5$ years, respectively, after initial symptoms. However, the patient with the shortest survival time developed an unusual presacral tumour which, according to the criteria of Aguirre and Scully (1982), would be classified as a monodermal teratoma rather than as a peripheral neuroectodermal tumour. The other two patients, each with a tumour of the lower extremities, died despite local irradiation with 6,000 rads. Both developed lung metastases and exten-

sive osseous metastases to cranium, ischium, femur and ilium were found in one of the two. Almost all 31 patients in the study of Hajdu (1979) and 9 of 14 patients reported by Hashimoto et al. (1983) did not survive. Four of the seven patients under 18 years died. Survival of all patients varied between $2^1/_2$ months and 13.4 years. Pulmonary metastases were noted in all five patients, in whom metastases could be confirmed at clinical follow-up.

Prognosis is also poor for most patients with "Askin tumour" (Askin et al., 1979). Fourteen of 18 evaluable patients died with survival varying from 4 to 44 months. Among the metastatic sites the lungs were most frequently involved. The histogenetic relationship of "Askin tumour" to the type of tumour described by Barson et al. (1978) as "Chest wall sarcoma of childhood with a good prognosis" remains in question. Although these authors suspected an endothelial origin on the basis of ultrastructural findings, including pinocytic vesicles, it seems possible to postulate from their figures that these tumours were also of neuroectodermal origin. In one photograph (Fig. 5) they illustrate cytoplasmic processes with dense-core granules, but did not comment on them. Only one of the four children with this type of tumour died, while the others were alive 6, 8 and 16 years after presentation. Interestingly, survivors had tumours located on the anterior aspect of the chest wall and in the mid-zone, whereas the patient who died had a tumour which was located posteriorly. From these findings it is tempting to speculate on whether the precise location in the thorax where the tumour develops plays a crucial role in its biological behavior. It also remains open whether the paravertebral "round cell" tumours reported by Tefft et al. (1969) form a separate entity or represent malignant peripheral neuroectodermal tumours. Follow-up data in our study are still preliminary. Five of 12 patients on whom follow-up information was available died, two are alive with disease and another five patients are living without evidence of disease. As in other studies metastases occurred in lungs and bone.

Origin of MPNT from a major nerve is not evident in every case (Enzinger and Weiss 1983). None of our 17 cases appeared to originate from a peripheral nerve. Recently, Jaffe et al. (1984) described three neuroendocrine tumours located in bone and no other primary could be detected. Another source of origin might therefore be neural crest cells which have migrated during embryogenesis to peripherally located soft tissues. Tumours subsequently arising from these cells may show differentiation into ganglion cells (Bolen and Thorning 1980), although this has been disputed by others (Enzinger and Weiss 1983). Areas with histological features of ependymoma, astrocytoma, oligodendroglioma and ganglioneuroma may be present (Nakamura et al. 1982). Two of our cases contained ganglion cells, in another tumour we saw Flexner rosettes and tubular structures. Similar findings were described by Stout and by Loycke (see Schmincke 1956). Further evidence suggesting different stages of differentiation is provided by the results of our immunohistochemical examination for intermediate filaments. We were able to show that these lesions may contain only vimentin or neurofila-

ments. In rare instances, however, they may express both types of intermediate filaments, in addition to glial fibrillary acid protein (GFAP). Since production of vimentin precedes formation of neurofilaments during embryogenesis (see Osborn and Weber, 1983) tumours presenting both vimentin and neurofilaments or neurofilaments alone are better differentiated than the relatively primitive vimentin-containing tumours. Positivity for GFAP in the case containing three types of intermediate filaments even demonstrates the possibility of differentiation into glial or ependymal structures.

In conclusion, it is evident that MPNT's, including "Askin tumours", constitute a homogeneous group. Variations in expression of intermediate filaments and in PAS-reactivity may be attributed to varying grades of differentiation and/or quality of preservation of the tumour tissue (fixation). The group of thoracic Ewing's sarcoma has become smaller, but Ewing's sarcoma as an entity still exists. The most important criterion for ruling out Ewing's sarcoma in differential diagnosis is a positive reaction for NSE.

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