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Peripheral Medulloepithelioma

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Summary. A case of congenital peripheral medulloepithelioma arising in the sciatic nerve of a 6-month-old boy is reported. Histologically, areas of primitive neural tumor merged with areas showing differentiation into ependymoma, astrocytoma, oligodendroglioma, and ganglioneuroma. These lines of differentiation were confirmed by electron microscopy and immunohistochemistry. Despite the malignant nature of the tumor, 7 years after amputation of the affected leg, the child is alive without recurrence.

Key words: Medulloepithelioma – Peripheral nerve – Congenital

Medulloepithelioma is a rare, malignant tumor recapitulating embryonic neural tissue in that patterns resembling primitive medullary plate and neural tube predominate. Usually, the tumor arises in a cerebral hemisphere. Although there have been several well-documented reports of cerebral medulloepithelioma (e.g. Deck 1969; Russell and Rubinstein 1977; Treip 1957), medulloepithelioma of peripheral nerve has rarely been reported (Stout 1942). This paper reports a case of a congenital peripheral medulloepithelioma arising in the sciatic nerve and showing a wide range of neuroectodermal differentiation.

Material and Methods

Tumor tissue was obtained from both biopsy and amputation specimens. The lesions were extensively sampled.

For light microscopy, representative portions were fixed in 10% buffered formalin, dehydrated, embedded in paraffin, and cut into 5 μm thick sections. Sections were stained with hematoxylin and eosin (HE), periodic acid Schiff (PAS), Mallory's phosphotungstic acid-hematoxylin stain (PTAH), luxol fast blue (LFB), Bielschowsky's stain, Masson trichrome stain, cresyl violet, and mucicarmine.

Paraffin-embedded sections were used for the peroxidase anti-peroxidase (PAP) method of Sternberger (1970). Each slide was stained with rabbit GFAP antisera in a 1:300 dilution (Eng et al. 1971). Pre-immunization rabbit serum diluted 1:300 was used as a negative control.

For electron microscopy, small tissue fragments were fixed in glutaraldehyde, postfixed in 2% osmium tetroxide, dehydrated, and embedded in Epon. Thick sections were stained with toluidine blue and thin sections with uranyl acetate and lead citrate.

Case Report

A 6-month-old boy was admitted to The Hospital for Sick Children, Toronto, for investigation of a soft tissue lesion on the dorsum of the right foot and another mass in the right leg posterolaterally just distal to the knee. The baby had been the product of a normal pregnancy, labor, and delivery. At birth, the right foot was noted to be malformed and, on the dorsum, a mass lesion was present and partially excised at another hospital. The developmental milestones were normal.

Physical examination showed an active, healthy, 6-month-old boy. Head, neck, chest, and heart were normal. The abdomen was soft and non-tender with no masses. No cervical, axillary, or inguinal nodes were palpable. There was no organomegaly.

Examination of the right leg showed a large, soft, subcutaneous (s.c.) mass in the posterolateral aspect of the leg extending from the ankle to the knee. Apart from the restriction of movement due to the tumor mass, the baby had a full range of movement at the hip, knee, and ankle. A scar was present over the dorsum of the foot. Two middle toes were absent and the lateral two toes were fused. The foot was slightly curved inward (Fig. 1, inset). There was no detectable loss of sensation over the foot.

Hematology, bone marrow, VMA clearance, electrolytes, alkaline phosphatase, and SGOT were all within normal limits. A body scan showed increased uptake in the right foot and leg corresponding to the soft tissue lesion. The renal scan showed non-function of the right kidney and its absence was confirmed by IVP. Roentgenogram of the affected limb showed absence of two metatarsals and abnormally small, residual metatarsals and phalanges. There was no other evidence of skeletal abnormality.

A biopsy was taken from the tumor on the right foot. Six weeks later, the baby was re-admitted because the mass in his right leg had increased, and tumors were now evident in the thigh and buttock. A laparotomy showed no intra-abdominal tumor. A right hemipelvectomy was performed. No chemotherapy or radiotherapy was administered.

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Results

Gross Findings

The excised specimen included the right leg and right half of the pelvis from close to the midline of the sacrum to the symphysis pubis. There were several masses occupying the entire thigh and leg along the course of the sciatic nerve and its branches (Fig. 1).

A firm, pink mass $4 \times 4 \times 3$ cm was identified posteriorly near the surgical margin deep to the gluteus maximus (tumor A). This tumor was adherent to the pelvis from the iliac crest to the posterior iliac spine and along the lateral to the posterior border of the iliac crest. It was adjacent to the sciatic nerve but there appeared to be a natural plane of division between the tumor and the sciatic nerve on that side. The tumor appeared to infiltrate adjacent muscle fibres but did not involve the surgical margin.

A $3 \times 2 \times 1.8$ cm nodular tumor (tumor B) was adjacent to the lateral portion of tumor A at the superior end of the tumor. Tumor C was separate from tumors A and B; it measured $1.8 \times 1.5 \times 1.0$ cm and was situated deep to the inferior border of the gluteus maximus muscle. This mass extended away from the sciatic nerve in a posterolateral direction.

Tumor D, measuring $4 \times 2.8 \times 2.0$ cm, was in continuity with tumor C. It was lateral to and adjoined the sciatic nerve in the thigh region, and lateral and slightly deep to the semi-membranous muscle. Immediately distal to and in continuity with that mass was a fluid-filled, thin-walled cyst (tumor E) measuring $3 \times 2.7 \times 2.5$ cm. The contours of tumors C, D, and E were smooth and dissected freely away from surrounding connective tissue.

Tumor F was fusiform, measured 3×4.5 cm, and blended into another fusiform tumor (tumor G) at the inferior end at about the level of bifurcation of the sciatic nerve.

Tumor G occupied most of the posterior calf region and was deep to the gastrocnemius muscle. Its contours were generally fusiform but there were many nodular irregularities. Laterally, it was in continuity with the s.c. fat. Tumor G displaced the lateral belly of the gastrocnemius muscle which was markedly thinned overlying the tumor. The tumor extended posterolaterally to the peroneal muscle. The two branches of the peroneal nerve were adjacent to the tumor anterolaterally. The distal two-thirds of the main tumor was completely separate from any attachments to the medial popliteal or branches of the lateral popliteal nerve but the proximal third was attached to that nerve.

A small separate nodule (tumor H) was present medially at about the level of bifurcation of the sciatic nerve. On the dorsum of the foot was a healed scar 3.0×4.5 cm.

Two weeks after surgery, the patient was discharged. Seven years later, his combination prosthesis and brace fit well and he is walking independently. He has had no recurrence of the tumor.

Microscopic Findings

The neoplasm was composed of poorly differentiated and differentiated cells of neuroepithelial origin. The most notable histological pattern was that of rows of cells resembling the medullary plate and neural tube (medulloepithelioma). This primitive epithelium consisted of tall pseudostratified columnar cells with vesicular nuclei containing coarse chromatin and prominent nucleoli. There was a moderate amount of eosinophilic cytoplasm. Mitoses were numerous and confined mainly to the luminal surface of the neuroepithelial layer. Neither cilia nor blepharoplasts were identified. Both the luminal and external margins of this layer were covered by PAS-positive material. This neuroepithelial cell layer was surrounded by a mantle layer of poorly differentiated neuroectodermal cells and was not directly adjacent to the connective tissue. The neuroepithelial cells tended to form elongated slit-like cavities adjacent to the better differentiated glial tissue (Fig. 2), consisting mainly of astrocytoma and occasional oligodendroglioma areas. Ependymomatous differentiation was characterized by the formation of small ependymal rosettes showing cilia and blepharoplasts with the PTAH stain (Fig. 3). There was also poorly differentiated tumor with round-to-oval, dark nuclei and scant cytoplasm, similar to medulloblastoma. Numerous mitotic figures were found in these areas. Occasionally, Bielschowsky-positive fibrils were demonstrated in cells with nuclei containing prominent nucleoli (Fig. 4).

This histologically malignant tumor infiltrated the surrounding connective tissue in some areas and in other areas tumor cells partially surrounded and lay close to the sciatic nerve but did not show involvement of the nerve itself. There were no metastases to lymph nodes. GFAP was not demonstrated in the neuroepithelial cells or in the poorly differentiated areas of the tumor. On the other hand, GFAP was present in better differentiated areas (Fig. 5) of both astrocytic and ependymal origin.

Electron Microscopic Findings

Electron microscopic findings varied with the cell type. In neuroepithelial tissue, the cells had relatively little cytoplasm which contained few organelles (mainly free ribosomes and mitochondria) and irregular-

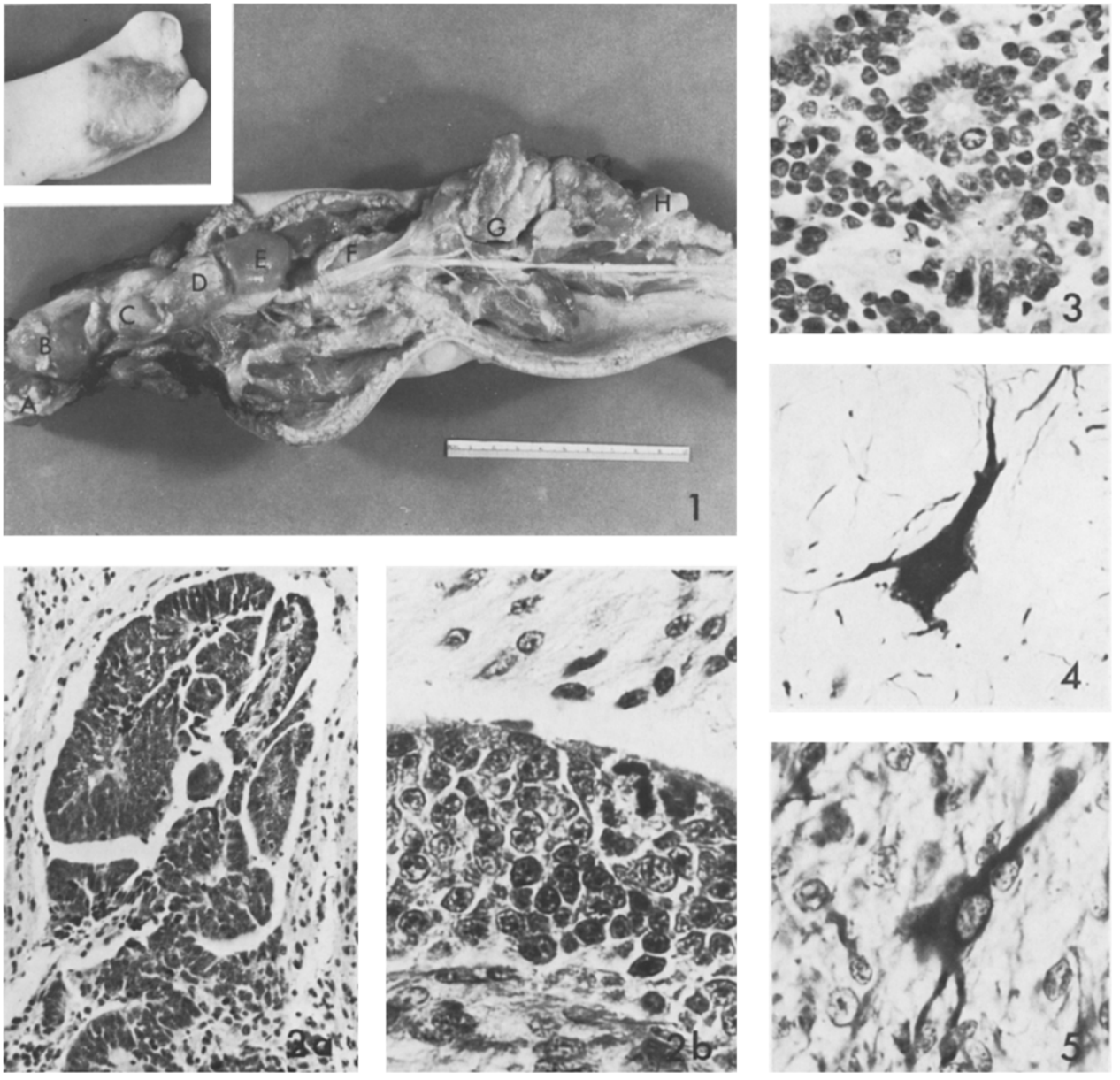

Fig. 1. Amputated specimen showing several masses in the thigh and leg along the sciatic nerve and its branches. *Inset:* Large scar over the dorsum of the foot and the malformed toes

Fig. 2.a Membrane-bound pseudostratified columnar cells forming structures that resemble the neural tube (HE, × 32). **b** Higher magnification of the neuroepithelium (HE, × 128)

Fig. 3. Area of ependymal differentiation showing formation of small ependymal rosettes (HE, × 64)

Fig. 4. Area of neural differentiation identified by the presence of neurofibrils (Bielshowsky's stain, × 128)

Fig. 5. Area of astrocytic differentiation identified by GFAP stain (× 128)

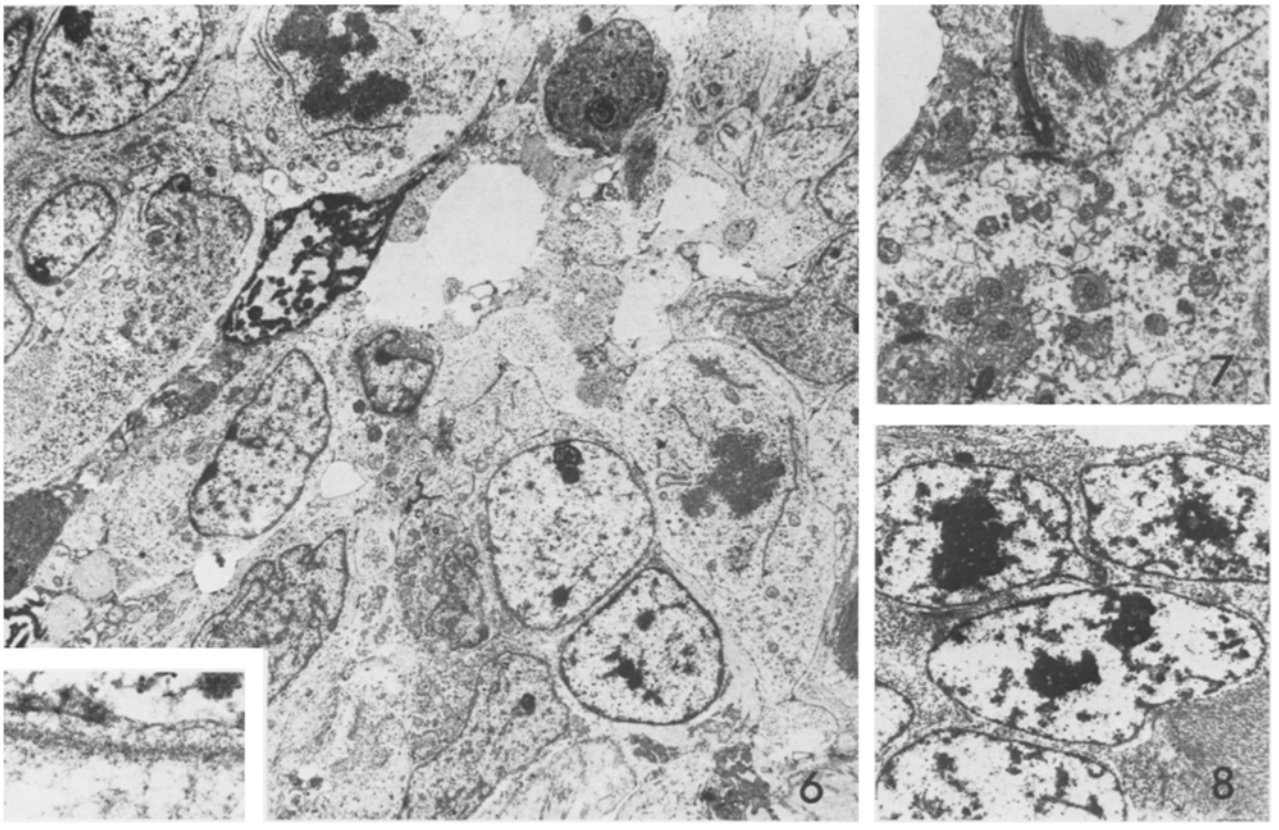

Fig. 6. Mitotic features, scattered organelles, junctional complexes, and finely granular surface coating in the neuroepithelium shown by electron microscopy (× 3,350). *Inset:* Basement membrane around the outer surface of neuroepithelium (× 80,000)

Fig. 7. Area of ependymoma showing cilia, centrosomes, and junctional complexes (× 8,750)

Fig. 8. Medulloblastoma cells with large nuclei containing prominent nucleoli and scant cytoplasm surrounded by glial cells (× 4,230)

shaped nuclei, which contained coarsely granular chromatin. Mitoses were frequent. An outer basement membrane was present but an inner limiting membrane was not; instead, there was an amorphous material partly surrounding the lumen. Cell junctions were found at the lateral margin of the cells near the surface of the epithelium. These junctional complexes were devoid of tonofilaments (Fig. 6).

In the area of ependymomatous differentiation, numerous microvilli and occasional cilia projected from the cell surface. Centrosomes could be identified just below the surface of the cell. There were many junctional complexes along the lateral margins, all of which lacked tonofilaments. The cytoplasm was rich in mitochondria, rough endoplasmic reticulum, and free ribosomes (Fig. 7).

In other areas, there were astrocytes containing glial fibrils and medulloblastoma-like cells which had large nuclei with prominent nucleoli and scant cytoplasm (Fig. 8). No oligodendroglia or neuronal elements were present in the tissue submitted for electron microscopy.

Discussion

Medulloepithelioma, an extremely rare tumor usually arising in the cerebral hemispheres, is believed to be derived from the primitive medullary plate and neural tube. Since it was originally classified by Bailey and Cushing (1926), a few cases have been recorded that appear to fulfil the criteria of these authors. All the well-documented cases have occurred in children, ranging in age from infancy (Treip 1957) to adolescence (Dastur and Lalitha 1969).

The tumor has a distinctive microscopic appearance, although several different patterns of differentiation may be observed. The characteristic feature which must be present is the "neuroepithelium", i.e., the arrangement of cells into stratified tubular or papillary structures with a sharply defined external limiting membrane and internal PAS-positive

material simulating an internal limiting membrane Mitoses are often numerous, particularly in cells adjacent to the internal lumina. In such neuroepithelium, neither cilia nor blepharoplasts are usually found. Using electron microscopy, Pollak and Friede (1977) found that the fine structure of the tumor is similar to that of the fetal neural tube since it has uniform nuclei which are rich in chromatin, with little cytoplasm, few organelles, a distinct basement membrane, lack of cilia or microvilli at the epithelial surface, an irregular amorphous covering around the internal lamina, and primitive forms of cell junctions.

From the morphological point of view, medulloepithelioma is the clearest example of a multipotential neural embryonic tumor. The spectrum of histology is explained on the basis of proposed differentiation from a primitive medullary plate and neural tube. Fujita (1965) postulated three successive stages of central nervous system (CNS) cytogenesis: first, the formation of matrix cells; second, differentiation into neuroblast; and third, differentiation into glioblast and ependymal cells. From this developmental standpoint, medulloepithelioma displays all the components of CNS differentiation.

Several cases with such multiple divergent neuroepithelial differentiation have been reported: areas of ependymoma, astrocytoma, and mature ganglion cells (Deck 1969); ependymoma and astrocytoma (Fowler 1968; ependymoma, astrocytoma, and oligodendroglioma (Karch and Urich 1972); and an entire range of differentiation from embryonal to mature cells (Scheithauer and Rubinstein 1979).

Another recognized site of medulloepithelioma is the eye, where the tumor has arisen from the primitive non-pigmented epithelium of the ciliary body and has been interpreted as the homologue of the cerebral medulloepithelioma (Russell and Rubinstein 1977). In this tumor, Andersen (1962) described areas of multipotential differentiation and formation of cartilage, usually in hyalinized mesenchymal tissue. This tumor has a rather benign character as compared to that of the brain.

A few exceedingly rare, malignant neoplasms have been reported under the name of medulloepithelioma or neuroepithelioma arising in peripheral nerve (Stout and Murray 1942; Bolen and Thorning 1980). These cases have features resembling neuroblastoma, showing Homer-Wright-type rosettes or undifferentiated round cells. Only one case (Cohn 1928) illustrates a suggestive neuroepithelium and this occurred in a patient with von Recklinghausen's disease.

The tumor in this case report was multicentric and located along the sciatic nerve and its branches adjacent to but not within the nerve itself. The tumor is likely to have been present from early embryonic life, as it apparently interfered with development of adjacent bones of the foot, resulting in the previously described deformity.

One may speculate on how the tumors assumed their peculiar distribution. Possibly embryonic CNS tissue was carried from the CNS during development of the sciatic nerve and developed into tumors along the course of the nerve.

A second possibility is that the primary tumor may have been distal and that the tumor spread along the perineural lymphatics. This might explain why the most proximal of the tumors appeared latest, was growing most rapidly late in the course, and was the least differentiated histologically.

In spite of the diagnosis of malignancy based on rapid growth, numerous mitotic figures, and tendency to infiltrate surrounding tissue, the child is alive 7 years after amputation. Thus, it appears that in the case of a peripheral medulloepithelioma, radical surgery to remove all tumor tissue is justified.

In summary, this is a case report of a well-documented, congenital, peripheral medulloepithelioma which has true neuroepithelium and multiple divergent differentiation into ependymoma, astrocytoma, oligodendroglioma, and ganglioneuroma.

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