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V-5A. Intraneural perineurioma/localized hypertrophic neuropathy

Intraneural perineurioma (IPN) is still referred to as localized hypertrophic neuropathy (LHN) (see above). Older, inexact terms, such as intraneural neurofibroma, hypertrophic neurofibrosis, and hypertrophic interstitial neuritis, have virtually been abandoned. IPN/LHN is rare and, according to some authors 1-3, the case described in 1964 by Da Gama Imaginário et al. 4 is credited as the first example on record. We have collected 73 cases from the literature 1-39, based on previous reviews for the period from 1965 up to 1996 2, 3, 28, 32, 40, and on electronic bibliography search (pubmed) for the period from 1993 to the end of 2004. We included all cases which were published as such, but some would be excluded because of insufficient data. But we did not include some other cases 40-46 which proved to be exemplary cases of localized “true onion-bulb neuropathies” and which must be kept separate from true IPN/LHN (see below at differential diagnosis). Although several pathogenetic stimuli have been involved in the past (e.g., trauma, microtrauma, ischaemia, inflammation, genetics, …), a neoplastic origin is now virtually unanimously accepted.

Clinical Findings

Males and females are equally affected. IPN/LHN mostly involves equally isolated major peripheral nerves of the upper and lower extremities 2,24. Cranial nerves are rarely involved 3. Uncommonly, there has been bilateral symmetrical involvement 37, including an instance of two simultaneously involved ipsilateral nerve roots (case 7 of Emory et al. 2). In the series of 8 cases contributed by Emory et al. in 1995 2 and from the critical review analysis they performed on the 26 likely cases since published, the patients' ages ranged from 9 to 42 years. Young adults are more often affected, but the disease has also been observed in infancy 30, 36 and in elderly. 13 In the series of Emory et al. 2, in descending order of frequency the affected peripheral nerves are the posterior interosseus, median, sciatic, tibial, brachial plexus, ulnar, radial, peroneal, femoral, and digital. Motor symptoms are constant, sometimes accompanied by sensory disturbances: weakness, neurogenic muscle atrophy, nerve palsy, sensory loss, Tinel’s sign, and focal tenderness may be present. Symptoms related to peculiar anatomical locations, e.g., carpal tunnel syndrome 21, 30 are recorded. In one case a small unnamed nerve involvement has been documented 33 and in another cases an intrasosseous location (e.g., lower jaw bone 35) has been observed. A localized mass is commonly found. The duration of symptoms has ranged from a few months to several years (up to 30 years 13) with a mean of 76 months in the series of 15 patients reported by Gruen et al. in their 15-year experience 24. Family history or association with neurofibromatosis/NF-1 have not been reported. Clinically and intraoperatively a fusiform peripheral nerve enlargement forming a localized rope-like mass is a constant finding (Fig. V-5Ai). The size of the lesions has ranged from approximately 1 to 30 cm (mean, around 5-6 cm).
**PATHOLOGICAL FEATURES**

The surgical specimen of IPN/LHN usually is represented by a small fascicular biopsy. Histologically, IPN is composed of concentric layers of spindle cells forming pseudo-onion bulbs (Fig. V-5Aii), often surrounding myelinated or unmyelinated axons. Increase of the interstitial collagen may be seen. In a unique case, a partially reticular pattern – similar to the one described in EPN – has been noted in association with the usual pseudo-onion-bulb pattern, typical of IPN.

**IMMUNOHISTOCHEMISTRY, ELECTRON MICROSCOPY, AND SPECIAL STUDIES**

The proliferating cells are immunoreactive for EMA (Fig. V-5Aii: inset) and vimentin and are negative for S-100 protein, CD34, desmin, and actins. Ultrastructurally, the specific fine features of the perineurial cells, such as slender cytoplasmic processes with discontinuous basal lamina, occasional tight junctions joining terminal cell processes, and numerous peripheral pinocytotic vesicles are usually visible and allow a confident diagnosis (Figs. V-5iii, V-5iv).

Cytogenetic studies and FISH analysis may demonstrate diverse abnormalities of chromosome 22 most commonly, or chromosome 142 35. Chromosome 22 is also involved in several other tumors of neuroectodermal origin (e.g., schwannoma, neurofibroma, meningioma, glioma), including soft tissue perineurioma (see the appropriate section).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis is twofold, clinically and pathologically. Pathologically IPN/LHN is to be differentiated mainly from diffuse hypertrophic neuropathies. Diffuse hypertrophic neuropathies are characterized by the intraneural formation of onion bulbs, i.e. laminated or concentric structures composed of EMA negative and S-100 protein positive proliferating Schwann cells, encircling axons, and causing multiple enlargement of peripheral nerves. The prototypical forms of diffuse hypertrophic neuropathies are represented by the hereditary and diffuse motor-sensory polyneuropathy (HSMN) type I or Charcot-Marie-Tooth disease, hypertrophic form, and HSMN type III or Dejerine-Sottas disease 47. However the family history, the clinical and molecular findings as well as the histologic, immunophenotypical and ultrastructural features enable the correct diagnosis. In our view, onion bulbs made of proliferating Schwann cells and their processes may well be called "true onion bulb neuropathies". True onion-bulb formations are also seen in other systemic, genetic, metabolic or degenerative conditions, such as Refsum disease, Krabbe’s disease, Roussy-Levi disease, metachromatic leukodystrophy, neurofibromatosis type 1, and diabetic neuropathy as well as in acquired diseases such as chronic inflammatory (demyelinating) poly(radiculo)neuropathy. Finally true onion-bulb formation may also be seen in some other rare localized diseases, such as “(localized) hypertrophic inflammatory neuropathy” 48, which additionally is characterized by the presence of intraneural mononuclear inflammatory cell infiltrates, and “localized true onion-bulb neuropathy”. “Localized true onion-bulb neuropathy” is a non-inflammatory hypertrophic neuropathy, equaling histologically the classic diffuse hypertrophic neuropathy but affecting single nerves either spinal nerves 40 41 or cranial nerves 40-44, which still awaits a definite categorization. Localized true onion-bulb neuropathy might even represent a fruste incomplete expression of diffuse hypertrophic neuropathy, which may later on manifest in its complete expression. Unfortunately “localized true onion-bulb neuropathy” is currently known under the term of localized hypertrophic neuropathy 40 41-44, which although semantically correct is unfortunately misleading in practice since, as previously stated, this same term is also synonymic with IPN.

IPN/LHN may also enter the differential diagnosis of EPN 48, but EPN is a tumor mass not associated with peripheral nerves, and its various histologic varieties (see the appropriate section) are distinct from IPN/LHN. Further, axons are present in IPN/LHN but not in EPN. Another entity, of very recent description, which might be considered in differential versus IPN/LHN, is represented by intraneural dendritic cell neurofibroma with pseudorosettes 49: the only case so far reported of intraneural dendritic cell neurofibroma with pseudorosettes 49: however the family case so far reported of intraneural dendritic cell neurofibroma with pseudorosettes exhibited a pleomorphic intraneural growth pattern involving several nerve twigs and is S-100 protein positive. Further, pseudorosettes which typify this latter entity can be easily distinguished from pseudo-onion bulbs of INP/LHN even on morphological grounds. Clinically IPN/LHN may be confused with several other mass-forming neural lesions including fibrolipomatous hamartoma, lipoma, angioma, and neuropathic amyloidosis, all of which are easily distinguished histologically.

**BIOLOGICAL BEHAVIOUR**

IPN/LHN is benign and malignant transformation has not been observed. Preservation of neural integrity should be the goal of treatment. For advanced cases, resection with autologous interposition graft repair has been proposed 2.

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Soft tissue perineurioma (STPN) is the term coined for a soft tissue tumor composed of cells showing perineurial differentiation. According to Lazarus and Trombetta, who first reported the entity in 1978, STPN represented a third category of peripheral nerve sheath tumors along with schwannoma and neurofibroma. Subsequently, the terms storiform perineurial fibroma and extraneural perineurioma (EPN) have also been used interchangeably to describe this lesion (see above at the Background section).

A computerized bibliography search (pubmed) from 1978 to the end of 2004 year revealed 144 cases of benign STP/EPN in the literature, albeit not all fully documented. In the critical review of Giannini et al., up to 1997, only 13 cases were considered genuine STP/EPN out of 22 cases since reported as such.

**CLINICAL FINDINGS**

STPN/EPN usually presents as a well circumscribed soft tissue tumor mass, arising mainly in the subcutaneous tissues or subfascial planes of limbs and trunk of young and adult individuals, which unlike IPN is not associated with a peripheral nerve, even though it may occasionally lie adjacent to it. Both sexes are affected, predominantly females (female to male ratio around 2:1). Patients are usually adult (median age around 45 years), but pediatric cases are also on record. STP/EPN usually occur in the skin as well as in superficial and deep soft tissue. However, intraoral (case 2 of a series of 6) and paranasal intrasinusal, intraosseous, retroperitoneal soft tissue, and visceral locations have also been observed. Visceral locations of STPN/EPN have been mainly renal both in childhood, ocassioning the clinically difficult differential diagnosis of Wilms’ tumor, and also adulthood. A unique intraventricular case in the central nervous system is on record, having histological, immunophenotypical and ultrastructural similarities to the soft tissue analogues. Symptoms are mass related. No motor-sensory disturbances have been recorded. Most STPN/EPN are less than 4 cm in size, with a range from 3 mm to several cm, including a giant form of 20 cm. Acral sites, mainly hands and digits, are often involved, and one case involved the hands bilaterally. The face is uncommonly involved. Almost unique occurrences are those in the breast, external auditory canal, and external male genitalia.

**PATHOLOGICAL FEATURES**

Grossly the tumor is well-circumscribed but unencapsulated. The consistency varies from rubbery and firm to soft. On cut surface the color is whitish to grey. Some examples, particularly the renal forms, are myxoid. Histologically several types of STPN/EPN have been described. The case of Lazarus and Trombetta still remains the prototype of the conventional form. Subsequently striking microscopical variations have been reported of this tumor, such as the fibrous/sclerosing, retiform or reticular, sclerosing pacinian-like, psammomatous, and lipomatous. Transitional or combined forms may be apparent as well. The conventional form consists of spindle or elongated cells, often arranged in parallel or as intersecting fascicles with occasional storiform arrangements. Fibrous, hyalinizing or myxoid changes of stroma may occur. Distinctive cellular arrangements include tactile-corporcular-like structures and pseudo-onion bulb or Verocay-like body arrangements. The prominence of any of these latter histological aspects allows the qualification of some of the aforementioned variants. Psammomatous calcifications are seen only occasionally and metaplastic ossification has been seen only once. Some histological subtypes are more often seen in peculiar locations, such as the sclerosing variant in the hands and digits and the pacinian-like variant in the digits. A unique case of STPN/EPN with granular cell changes has also been described and one case of sclerosing perineurioma with prominent collagen rosettes has also been observed. The retiform and the plexiform variants were so termed, following the architectural pattern of the tumor growth, while the lipomatous variant contains an adipose tissue component. Finally, hybrid or composite forms with histological and immunophenotypical features of both STP/EPN and schwannoma, as well as STPN/EPN and neurofibroma, have recently been reported in extradigital and digital locations.

Atypical forms and malignant examples of STPN/EPN have been occasionally encountered, identified by cellularity and nuclear atypia in the former category, and additionally by mitoses and necrosis in the latter.

**IMMUNOHISTOCHEMISTRY AND ELECTRON MICROSCOPY**

Immunohistochemically STPN/EPN is like its intraneural counterpart – vimentin and EMA positive.
V-5Bii) and negative for S-100 protein, CD57, synapthophysin, desmin, actins, FXIIIa). CD34 is usually negative, but may be focally positive in some cases or even occasionally diffusely positive 37. Collagen IV is sufficiently detectable in a pericellular distribution, but laminin is weakly expressed 50. New adjunctive immunomarkers include claudin-1 42, a member of the protein family involved in the formation of tight intercellular junctions, and GLUT1 45, the human erythrocyte glucose transporter antigen.

Ultrastructurally STPN/EPN is mainly or solely composed of cells showing perineurial differentiation, i.e., slender cytoplasmic processes coated by a discontinuous external lamina, tight junctions uniting the ends of cell processes, few cytoplasmic organelles, vimentin filaments, and numerous pinocytotic vesicles 63 (Figs. V-5Bii, V-5Biv). Many authors employed electron microscopy in the study of their cases. In two cases ribosome-lamella complexes have been seen 15, 50. These have also been described in another ST tumor, the ossifying fibromyxoid tumor, a neoplasm which is also suggested to exhibit neural differentiation. Immunohistochemistry and electron microscopy serve as essential tools also for the diagnosis of STPN/EPN, and both immunohistochemistry and ultrastructural findings are – as previously said – similar to those observed in IPN.

Special studies
FISH analysis demonstrated an abnormality of chromosome 22 even in STPN/EPN 18, 36, similarly to what was previously described in INP/LHN, a fact that “supports” the view that both STPN/EPN and INP/LHN are part of the spectrum of perineurial neoplasia. Clonal chromosomal abnormalities of chromosome 10 and a cryptic deletion of the 5'BCR and NF2 loci on chromosome 22 were found in a cytogenetic and molecular study 39.

Differential diagnosis
Many diverse tumors enter the differential diagnosis, in accordance with the numerous histological types of STPN/EPN. The conventional type is to be distinguished from a wide spectrum of spindle cell tumors and tumor-like lesions, including neurofibroma, schwannoma, solitary encapsulated neuroma, neuroblastoma-like neurilemmoma, neuroblastoma-like epithelioid schwannoma, dermatofibroma, nodular fasciitis, nerve sheath myxoma, tendon sheath fibroma, subcutaneous fibrous meningioma, dermatofibrosarcoma protubersans, solitary fibrous tumor, myoepitheliomas 66, 68, low grade myofiobrosarcoma 70, 71, low grade peripheral nerve sheath tumor, and monophasic synovial sarcoma.

The fibrous or sclerosing (also called hypocellular or collagenized form) needs to be differentiated from fibroma-NOS, desmoid tumor, desmoplastic fibroblastoma (collagenous fibroma) 72, circumscribed storiform collagenoma (sclerotic fibroma) 73 and solitary fibrous tumor (hypocellular variant).

The myxoid form needs to be distinguished from low-grade myxofibrosarcoma, low grade fibromyxoid sarcoma, and myxoid dermatofibrosarcoma protubersans. The pacinian-like variant of STPN/EPN, usually occurring in superficial sites of the hands and digits, is considered by some authors as the same entity as the pacinian neurofibroma of the older literature 74, 77. The plexiform variant, which is also commonly myxoid, must be differentiated from neurothekeoma, and in fact some examples of the latter probably represent misdiagnosed cases of STPN/EPN of the plexiform type. The retiform or reticular form has an architectural pattern mimicking ossifying fibromyxoid tumor 81 and extraskeletal myxoid chondrosarcoma 82, which need to be excluded.

The lipomatous perineurioma should be considered in the differential diagnosis of both spindle cell mesenchymal and neuroectodermal tumors that contain an adipocytic component, such as spindle cell lipoma and spindle cell liposarcoma among the former, and lipomatous neurofibroma among the latter 53, 84.

However, the correct diagnosis rests foremost on awareness of this entity, which – despite its protean, histological appearances, has a remarkably constant immunoprofile and ultrastructural appearance. Practically none of the differential diagnostic considerations listed above has such a simple immunoprofile, except for the rare occurrence of a fibrous or transitional type of ordinary meningioma, which may be encountered especially in the head and neck area as an heterotopic event or as a transosseous penetration from a meningeal based tumor. In this latter situation, electron microscopy can ascertain the meningotheliomatous differentiation by showing complexly interdigitating processes, intercellular desmosomes, lack of pinocytotic vesicles, abundant intermediate filaments and lack of external lamina. However caution must be exercised since several tumor-like conditions and genuine tumors in the schwannoma/neurofibroma spectrum may express EMA in a proportion of cells, the latter interpreted as reactive 1, 2, 3, 5. Neurofibroma might be the most likely diagnostic pitfall, due to the participation not only of several distinct cell types in this tumor, i.e., Schwann cells, perineurial cells, and fibroblasts, but also of intermediate cells, having overlapping ultrastructural and immunophenotypic features, i.e., hybrid Schwann-perineurial cells and fibroblast-perineurial cells. Some neurofibromas do exhibit a predominantly ultrastructural perineurial cell differentiation or show a prominent immunohistochemical perineurial cell component 54. There is a case published as a perineuroma 11, comprehensively studied by multiple modalities, which was excluded as a perineuroma after critical revision by others, who interpreted the tumor as a likely perineurial cell-rich neurofibroma 18. A further case is on record which was interpreted as a likely perineurial cell-rich neurofibroma by its authors, which showed the typical immunoprofile of...
Schwann cells on one hand and ultrastructural features of perineurial cells on the other. Ultimately, STPN/EPN may also enter the differential diagnosis of dendritic cell neurofibroma with pseudorosettes, the latest described variant in the neurofibroma spectrum, of which even an intraneural subtype has also been recognized: however, dendritic cell neurofibroma with pseudorosettes is S-100 protein positive (and EMA negative) and is typified by pseudorosettes, which are absent in STPN/EPN.

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V-6. Superficial (cutaneous and subcutaneous) Ewing’s sarcoma

Ewing’s sarcoma is primarily an undifferentiated small round cell tumor of bone, representing in order of frequency the fourth neoplasm in this location, after myeloma, osteosarcoma, and chondrosarcoma in general and the second most common primary osseous malignancy in childhood and adolescence after osteosarcoma. Ewing’s sarcoma also occurs (10% of cases) as a primary tumor in soft tissue without involvement of bone (primary extraskeletal Ewing’s sarcoma). Ewing’s sarcoma and peripheral primitive neuroectodermal tumor (EWS/pPNET), including primitive neuroepithelioma, are neoplasms of the same family (Ewing family of tumors), the former tumor without and the latter with neural differentiation. EWS/pPNET comprises around 1% of soft tissue tumors in general; the most common location are the deep soft tissues of the lower extremities (including the perineal space), the paravertebral region, the retroperitoneum, and the intraabdominal cavity (pelvis, peritoneum, diaphragm). Rare visceral locations are also on record (kidney, pancreas, uterus, larynx). Very rarely it occurs in the skin and subcutaneous tissues (superficial EWS/pPNET) with forty-five cases of primaries reported so far 1-17. The first report of three cases is due to Angerwall and Enzinger and dates back to 1975 1. Up to 1995 all cases were studied by light microscopy alone, with the only support of electron microscopy in some. In the years 1995-1997, cutaneous and subcutaneous EWS/pPNET were published, which were additionally studied by immunohistochemistry 11-13, and in 1998 the first cases corroborated by molecular genetic investigations also appeared 14. From all these investigative techniques documentation derived that superficial EWS/pPNET has the same morphology, immunophenotype and molecular abnormalities as seen in bone and deep soft tissue counterparts.

CLINICAL FINDINGS

Children and young people are usually affected 13 14 16, but less often superficial EWS/pPNET also occurs in adulthood with six such total cases on record 1 4 7-9 13 17. Congenital cases may also be encountered (MB, unpublished personal observation of two cases). Both sexes are affected. In order of frequency, anatomic locations include lower limbs, trunk (chest and abdomen) and pelvis, head (mainly the scalp) and neck, and upper limbs 13 14 17. A case of EWS/pPNET of the breast is also on record 18. The main sign in cutaneous and subcutaneous locations is represented by a solitary nodular lesion, sometimes with polypoid appearance, often clinically misinterpreted as an adnexal skin tumor or even a trivial lesion (hemangioma, pyogenic granuloma, dermoid or trichilemmal cyst). In none of the published cases of superficial EWS/pPNET, evidence of tumor at other locations was found.

PATHOLOGICAL FEATURES

Grossly, the tumor is most often described as a solid, well circumscribed, but unencapsulated, nodular mass, ranging in size 1 to 10 cm. On cut section it is described as a greyish-white and fleshy nodule. Foci of hemorrhage are often visible. Histologically, the growth pattern may be compact as well as retiform (due to dyscohesion of cells), or microcystic or frankly pseudocystic. Rosettes of the Flexner-Wintersteiner type have been seen in one unique case of congenital superficial EWS/pPNET (personal unpublished observation of one (MB) of the authors). The tumor is composed by undifferentiated small round cells, with scanty to moderate glycogen-rich cytoplasm, and vesicular nuclei, with few to many mitoses Fig. V-6i→V-6iii.

IMMUNOHISTOCHEMISTRY

Immunohistochemically, tumor cells in superficial EWS/pPNET are usually positive for vimentin. Occa-
tionally, rare cells may express cytokeratins. Muscle markers are negative, but desmin has been seen as a divergent expression in one study and interpreted as an indication of an overlapping phenotypic spectrum with (intraabdominal) desmoplastic small cell tumor, but was not confirmed in another; all endothelial markers are always negative as negative are lymphoid and myeloid markers. Some neural/neuroendocrine markers (including S100-protein, NSE, neurofilament proteins, PGP9.5, synaptophysin, and Leu-7) have been found positive by some authors, but could not be confirmed by others, except NSE. In the latter report chromogranin was tested in one case only, and was also negative. For reference and comparison we would like to quote the results of an immunohistochemical study of 28 total cases of osseous (19 cases) and soft tissue (9 cases) EWS/pPNET: NSE was found in 17 cases, S-100 protein in 7, Leu-7 in 4 and neurofilament proteins in 2, while chromogranin was never detected; and the investigators of the last study – according to the expression of the number of neural markers – categorized their cases in a three-tiered classification scheme of undifferentiated (no marker positive: 10 cases), poorly differentiated (1 marker positive: 12 cases) and well differentiated (2 markers positive: 4 cases) tumors. In all studies, similarly to their bone and deep soft tissue counterparts, practically all cases of superficial EWS/pPNET were positive for CD99/MIC2 antigen, the protein product p30/32 of the MIC2 gene, and the most reliable marker in defining EWS/pPNET diagnosis (Fig. V-6iv).

**Electron Microscopy**

Ultrastructurally, in EWS/pPNET the tumor cells are small with high nuclear to cytoplasmic ratio. The cytoplasm is organelle-poor with visible intermediate filaments of vimentin type. Glycogen is usually abundant either in pools or in dispersed particles. Neuroendocrine granules can often be observed (5 positive cases out of 7 studied in the report by Banerjee et al.). While chromogranin was never detected; and the investigators of the last study – according to the expression of the number of neural markers – categorized their cases in a three-tiered classification scheme of undifferentiated (no marker positive: 10 cases), poorly differentiated (1 marker positive: 12 cases) and well differentiated (2 markers positive: 4 cases) tumors. For comparison, in the previously referenced study, which also classified osseous and extrasosseous EWS/pPNETs according to three categories on the basis of the number of positive ultrastructural findings (neurosecretory granules and/or cytoplasmic processes), 8 tumors were undifferentiated, 14 poorly differentiated (expressing either neurosecretory granules in 8 or cytoplasmic processes in 6), and 4 well differentiated (expressing both). Interestingly, the poorly differentiated tumors predominated among the osseous forms, while the reverse occurred among the well-differentiated. No other specific specialized substructure has been ever found in EWS/pPNET of any location, such as myofilaments, sarcomeres, melanosomes.

**Special Studies**

In EWS/pPNET of classical osseous and extrasosseous sites, a specific genetic translocation may be demonstrated by molecular investigation, using usual cytogenetic technique as well as reverse transcription polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) techniques. A translocation at t(11;22) (q24;q12), fusing FLI1 and EW genes, can be identified in up to 85% of cases by usual cytogenetics and in up to 90% by RT-PCR. In approximately 9% of ES/pPNETs a variant translocation t(21;22) (q22;q12), fusing ERG and EW genes, is detectable, in absence of the former. Concerning with cytogenetic translocation in superficial EWS/pPNET in all cases so far tested, FISH analysis was used for this purpose and was always positive.

Anyway other types of translocations not involving the classical chromosome region 22q12 have been found in superficial EWS/pPNET: NSE was found in 17 cases, S-100 protein in 7, Leu-7 in 4 and neurofilament proteins in 2, while chromogranin was never detected; and the investigators of the last study – according to the expression of the number of neural markers – categorized their cases in a three-tiered classification scheme of undifferentiated (no marker positive: 10 cases), poorly differentiated (1 marker positive: 12 cases) and well differentiated (2 markers positive: 4 cases) tumors. In all studies, similarly to their bone and deep soft tissue counterparts, practically all cases of superficial EWS/pPNET were positive for CD99/MIC2 antigen, the protein product p30/32 of the MIC2 gene, and the most reliable marker in defining EWS/pPNET diagnosis (Fig. V-6iv).

**Differential Diagnosis**

As a member of the “small round-cell tumor” family the differential diagnosis of EWS/pPNET include a large variety of neoplasms, primary or secondarily involving the skin, of different lineages. In childhood mainly a metastatic involvement by peripheral neuroblastoma (“classic-type”), rhabdomyosarcoma (alveolar or embryonal types), or lymphoma and leukemia (including granulocytic sarcoma) should be considered. In one of the two congenital cases, we already mentioned, which was seen by several consultants, the differential diagnosis included among others also syновial sarcoma and infantile hemangiopericytoma. In adulthood, classically, metastatic undifferentiated or neuroendocrine small cell carcinoma along with primary cutaneous neuroendocrine carcinoma (Merkel cell tumor) and small cell amelanotic melanoma are the priorities; atypical glomus tumor and glomangiosarcoma might also be a possibility of consideration in differential. Noteworthily, we would like to emphasize the morphological resemblance of cutaneous and subcutaneous EWS/pPNET to some benign and malignant adnexal skin tumors, such as eccrine spiradenoma, because of the comprising small cells, vascularity and pseudocystic spaces: a highly misleading similarity which has been already brought to light by other authors. However, if immunohistochemistry is used, a confident diagnosis is reached because of the lack in EWS/pPNET of the main and specific immunohistochemical findings, which are usually present in the alternative diagnostic considerations, and conversely by virtue of the high sensitivity and good specificity of the CD99 expression in EWS/pPNET. However, CD99 expression can also be found in other tumors, including lymphoblastic lymphoma, rhabdomyosarcoma, neuroendocrine tumors, and
synovial sarcoma, all neoplasms which enter the differen-
tial diagnosis with EWS/pPNET. Peripheral neuroblastoma metastatic to skin may be very challenging both histologically and immunohistochemi-
cally. In dubious cases electron microscopy and molecu-
lar analyses (FISH testing as well as RT-PCR) can solve the problem by detecting the specific genetic aberrations. The clinicopathologic setting in these instances should also be helpful and in accordance with the histological diagnosis, bearing in mind that EWS/pPNET is consist-
ently a localized disease. Cutaneous and subcutaneous EWS/pPNET may also represent a metastatic seeding from bone or deep seated primary is even possible 26. Awareness of this unusual location of EWS/pPNET is mandatory for general surgical pathologist since this form of the disease may well occur in routine practice. Awareness may let the pathologist suspect the tumor and address to the correct diagnosis which can be defi-
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(In refs. 1-17 the actual number of cases of superficial EWS/pPNET per report is indicated in brackets).

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BIOLOGICAL BEHAVIOUR

Superficial (cutaneous and subcutaneous) EWS/pPNET is believed to be a favourable subset of an otherwise highly aggressive neoplasm, and there’s some slight evidence that superficial EWS/pPNET represents the more differentiated end of the spectrum (high rate of presence of neuroendocrine granules, evidence of microtubules, documented synaptic junctions and synaptophysin expression in some of the cases in the study of Banerjee et al. 13).

With the exceptions of those two cases, 21, 22, which showed a genetic translocation not involving the chromosone region 22q12, in none of the remaining cases a multisystemic spread has been found, and this may be the main reason for the good prognosis, since initial presentation has been demonstrated as the only predictor of sur-
vival in soft tissue EWS/pPNET in general. 26. Local sur-
gical excision followed by local radiotherapy and courses of systemic chemotherapy is the suggested multimodal treatment in this usually apparently localized disease 16.


V-1. Psammomatous melanotic schwannoma

Fig. V-1i. Spindled cells arranged in cellular whorls characterize this psammomatous melanotic schwannoma. Note the focal psammoma bodies on the right.

Fig. V-1ii. Psammomatous melanotic schwannoma with epithelioid cells arranged in lobules. Note the lymphocytes between tumor lobules. Psammoma bodies were sparse in this example.

Fig. V-1iii. Coarse melanin pigment in tumor cells and histiocytes.

Fig. V-1iv. Spherical to oval laminated calcospherites (psammoma bodies) range from a few to many.

V-2. Pigmented neurofibroma

Fig. V-2i. Some areas of pigmented neurofibroma can be hypercellular.

Fig. V-2ii. Wagner-Meissner bodies may be a prominent feature of pigmented neurofibroma.
V.3. Dendritic cell neurofibroma with pseudorosettes

Fig. V-2ii. Pigmented cells often have a morphology of bipolar dendritic cells.

Fig. V-2iv. Masson-Fontana silver impregnation method reveal cells with coarse pigmentation; the pigmentation may be only dust-like (left side of the picture).

Fig. V-3i. Dendritic cell neurofibroma with pseudorosettes: multiple pseudorosettes are the hallmark of the lesion.

Fig. V-3ii. Dendritic cell neurofibroma with pseudorosettes: a close-up view of pseudorosettes. Small, dark, lymphocyte-like cells (Type I cells) are arranged concentrically around larger cells, with pale-staining vesicular nuclei and copious faintly eosinophilic cytoplasm (Type II cells). Stellate extensions may be discerned in the cytoplasm of some of the type II cells.

Fig. V-3iii. Dendritic cell neurofibroma with pseudorosettes: pseudorosettes are often grouped within a lesion. Inset: scroll-like structure.

Fig. V-3iv. Intraneural dendritic cell neurofibroma with pseudorosettes: this tumor occurred almost entirely within the confines of the perineurium.
V-4. Epithelial Sheath neuroma

(The pictures are courtesy of T. Mentzel, M.D., and H. Kutzner, M.D., both Dept. of Dermatopathology, Friedrichshafen, Germany).

**Fig. V-3v.** Intraneural dendritic cell neurofibroma with pseudorosettes: EMA stains the perineurium that encircles the neoplasm.

**Fig. V-3vi.** Dendritic cell neurofibroma with pseudorosettes: slender dendritic extensions of the cytoplasm of the type II cells highlighted by S-100 protein. Note a spider-like appearance of these cells.

**Fig. V-4i.** Epithelial sheath neuroma: the superficial dermis contains several enlarged bundles of mature peripheral nerves surrounded by an epithelial sheath.

**Fig. V-4ii.** Epithelial sheath neuroma: the epithelial sheath is composed of squamous epithelium, with focal keratinization.

**Fig. V-4iii.** Epithelial sheath neuroma: a sparse infiltrate of lymphocytes and plasma cells is present around some of the neuroepithelial aggregations.

**Fig. V-4iv.** Epithelial sheath neuroma: perineural epithelial sheaths are cytokeratin positive.
V-5A. Intraneural perineurioma/localized hypertrophic neuropathy

Fig. V-5Ai. Rope-like tumoral enlargement of left ulnar nerve. Notice the secondary (neurogenic) muscle atrophy of the hypothenar eminence. The pictures are courtesy of E. Vigilante, M.D., Dept. of Orthopedics, Casa Sollievo della Sofferenza Hospital, S. Giovanni Rotondo, Italy.

Fig. V-5Aii. Fascicular biopsy of the (ulnar) nerve. Histologic picture. Numerous intraneural pseudo-onion bulbs made of perineurial cells, with collagen deposition. Inset: immunohistochemical positive stain for EMA. Axonal loss was also documented by immunohistochemical stain for neurofilament proteins (not shown).

Fig. V-5Aiii. Layers of spindle cells with tracts of external lamina-like material. Numerous pinocytotic vesicles are evident along the cytoplasmic processes of perineurial cells (arrows).

Fig. V-5Aiv. Higher magnification. Subplasmalemmal rows of pinocytotic vesicles are well visible.

V-5B. Soft tissue perineurioma/extraneural perineurioma

Fig. V-5Bi. Histology. Fibrous tumor mainly composed of slender spindle cells embedded in abundant collagen matrix.

Fig. V-5Bii. Immunohistochemical diffuse positive stain for EMA highlighting the long and thin innumerable cytoplasmic processes in the collagenized tumor background.
V-6. Superficial (cutaneous and subcutaneous) Ewing’s sarcoma

Fig. V-5Biii. Ultrastructural detail of a tumor spindle cell showing an external lamina and numerous subplasmalemmal micropinocytotic vesicles (arrows).

Fig. V-5Biv. A thin cytoplasmic process surrounded ensheathed on both sides by basal lamina and showing several pinocytotic vesicles, partly scattered and partly in clusters.

Fig. V-6i. Low power of a small round-cell tumor involving the dermis and the subcutis of the inguinal region in an old patient aged 64.

Fig. V-6ii. High power. Same lesion as the previous figure. Hypercellular tumor comprised of small and round cells with scanty cytoplasm. Nuclei have dispersed chromatin. A mitotic figure visible in the center.

Fig. V-6iii. PAS preparation. Tumor cells have diffusely glycogen-rich cytoplasm.

Fig. V-6iv. Immunohistochemical testing for CD99/MIC2 antigen. This case was also studied by electron microscopy which showed ultrastructural findings consistent with EWS/pPNET.