PERIPHERAL NERVE SHEATH TUMORS – THEN AND NOW

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THE PRE-STOUT ERA

At the time that Arthur Purdy Stout became interested in the field of tumors of the peripheral nervous system, and thanks to the work of J. Verocay, Antoni, Pio del Rio Hortega, von Recklinghausen, Pierre Masson and others, these tumors were generally placed into one of three major categories:

1) The solitary sporadic encapsulated spindle cell tumor variously called variously called neurinoma (by J Verocay, an Uruguayan pathologist, in 1908), lemmocyteoma, schwannoma, perineurial fibroblastoma and peripheral glioma. These various names reflecting the existing uncertainty about their cell of origin;

2) The tumor typically associated with von Recklinghausen disease, known as neurofibroma;

3) The malignant tumor of peripheral nerves, often arising against the background of von Recklinghausen disease and variously called malignant schwannoma and neurogenic sarcoma, this also reflecting the different views about its presumed histogenesis.

ARTHUR PURDY STOUT’S CONTRIBUTIONS

The subject of tumors of the peripheral nervous system was one of Stout’s main interests, as he makes clearly evident in his autobiographical work “Notes on the education of an “oncologic” surgical pathologist”. He tells us that his interest was awakened by the observation during the early days of his work as surgical pathologist, of a neuroepithelioma of the ulnar nerve and a ganglioneuroma of the posterior mediastinum, the latter forming an hourglass extension into the spinal canal. He remarked on the fact that his study of these lesions marked the beginning of his great interest in tumors of the peripheral nervous system, “which led to many other articles and studies and correspondence with many Americans and foreigners also interested in the subject.” Crucial to this development, he adds, was an invitation of the American Association for Research in Nervous and Mental Diseases to participate in their 1935 meeting, which was devoted to the subject of tumors of the peripheral nerves. Since this was his first “really important” assignment, he took stock of the situation and determined to be “as well prepared as possible”. He approached his assigned topic by reading all of the available articles that had been written about it and by studying all of the material they had recorded in the hospital. This story is very reminiscent of that of Pierre Masson, whose interest in melanocytic tumors was sparked by an invitation to talk at an International meeting on the subject, and the original observations he made by examining with an open mind his own material. Stout made excellent use of the opportunity by writing two articles, one on the benign solitary tumor of nerves and the other on the malignant tumors of peripheral nerves, both of them published in the now defunct American Journal of Cancer, and which met with a degree of interest that exceeded his expectations. He proudly remarked that these articles “codified the knowledge concerning these various tumors” and posed certain questions that led him to initiate several fruitful investigations with the aid of Margaret Murray, an expert in tissue culture techniques working in his laboratory.

In one of those articles, he recounts how he came up with the word “neurilemoma” for the benign solitary tumor that at the time was variously known as neurinoma, lemmocyteoma, schwannoma,
perineurial fibroblastoma and peripheral glioma. With the help of G F Laidlaw, a fellow pathologist, and Frank Vizetelly (Editor of the New Standard Dictionary), he “manufactured” the neutral term nerve sheath tumor into a word of Greek roots, i.e., neurilemoma. Alas, this was the source of “endless bickering” because many subsequent erroneously changed the word into “neurilemmoma”. Stout pointed out the fact that it should be spelled neurilemoma (with a single m) because the lem root comes not from lemma (as most people believed) but from eilema. He lamented the fact that it was “a long hard fight to put this across”, a fight – we should add – that ended many years later with the use of the more specific name of schwannoma.

Stout also belabored over the nature of malignant nerve sheath tumors, and engaged in a spirited discussion on the subject with other prominent pathologists of his time. He criticized James Ewing, of Memorial Hospital, for introducing the term neurogenic sarcoma, because he did not see how these tumors differed from any ordinary fibrosarcomas. In one of his articles he stated: “It is to be deplored that such a careful observer as Shields Warren has expressed the opinion that the neurogenic sarcoma is an entity that can be recognized” It is easy to read in between the lines in this uncharacteristically caustic comment by Stout, who is really saying “I am not too surprised that James Ewing thought this way, but Shields Warren ought to know better!”

He urged that the term neurogenic be dropped and fibrosarcoma of nerves substituted for it. Stout commented about these problems “stirring around” in his mind, with him “keeping them cooking continuously, each year making some headway along the road and on the whole with a fair degree of speed”. One of the major breakthroughs was the demonstration by Margaret Murray on the basis of her tissue culture experiments that the nerve sheath tumors were composed of schwann cells and not fibroblasts. The two cell types, Stout remarked, are so different from fibroblasts in tissue culture that they cannot be confused. At the same time that he was doing these fundamental studies, Stout did not disdain the publication of reviews on the subject and the occasional case report.

When the felicitous decision was made in 1946 to launch the publication of a series entitled “Atlas of Tumor Pathology” (the legendary A.F.I.P. fascicles), it was only natural for Stout to be asked to be a member of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council that was supposed to supervise this work. Alas, when the time came to select the authors of the various fascicles, Stout confessed being appalled at the “dearth of talent” that existed and greatly disheartened after they were chosen. He ended up being the main author of no less than four of those fascicles, the first of which was – not surprisingly – the one on Tumors of the Peripheral Nervous System, published in 1949 and sold for the modicum price of $0.60. Putting it all together, he comments, was the easy part. He was not prepared, however, to “the delays, disagreements, mistakes of the printer and engraver, the choice of paper, and government dilatory methods that prevented its final appearance for three long years”. When it did appear, he laments, it was in a form very far from what he had hoped for. This is an astonishing confession on a publication which is widely regarded as one of the most influential achievements in the literature on the pathology of human tumors.

The final and most amazing comment Stout makes in his autobiography is the statement that “there was really nothing original in all of my studies of the peripheral nervous system”. He adds that he spent a great deal of time just trying to codify them, and that “the only really new observations were made by Dr. Murray from her tissue cultures.” Stout concluded his account on the subject with this melancholy reflection regarding his publications on this and many other subjects: “Most of these things are scattered far and wide in different and sometimes obscure medical journals. If any of the ideas persist my connection with them will be lost and forgotten, inevitably this is the rule. One must take what satisfaction one can out of the doing and not be expected to be remembered for it.”

THE POST-STOUT ERA

The most significant developments in the field in the post-Stout era have been the following:
The characterization of schwannomas of the gastrointestinal tract (stomach, small bowel, colon and rectum) and the establishment of criteria for their differential diagnosis with GIST, greatly aided by their immunohistochemical profile: positivity for S100 protein, calretinin (in contrast to neurofibroma), calcineurin, basal lamina components (such as collagen IV), GFAP, and low-affinity nerve growth factor receptor (P75), and negativity for CD117. Morphologically, a lymphoid cuff with germinal centers typically surrounds three tumors, a feature rarely if ever seen in their usual soft tissue location.

The peculiar and potentially misleading finding that about 70% of retroperitoneal schwannomas are immunoreactive for the keratin cocktail AE1/AE3.

The description of schwannomas and neurofibromas with scattered large bizarre tumor cells having huge hyperchromatic nuclei, which may be misinterpreted as malignant (schwannoma and neurofibroma with atypia).

The fact that, contrary to conventional wisdom, intratumoral axons (demonstrated with neurofilament protein) can be found in the majority of schwannomas (especially the conventional and cellular types), and are therefore not restricted to neurofibroma, as formerly believed.

The description or rediscovery of several more or less distinct variants of schwannoma, including:

- Schwannoma with neuroblastoma–like rosettes (neuroblastoma–like schwannoma)
- Microcystic / reticular schwannoma, a variant with predilection for visceral locations
- Schwannomas containing clusters of granular cells
- Plexiform schwannomas, not to be confused with the more common plexiform neurofibromas
- Benign epithelioid schwannoma, much less common than epithelioid MPNST
- Benign glandular schwannoma
- Cellular schwannoma, a somewhat controversial entity characterized by a high degree of cellularity, often accompanied by nuclear atypia, mitotic activity, and focal necrosis
- Psammomatous melanotic schwannoma, a distinctive lesion that occurs as a component of the Carney syndrome and which often arises from the spinal nerve roots. As the name indicates, this tumor is characterized microscopically by the presence of melanin pigmentation and deposition of psammoma bodies. It is regarded as a low grade malignancy, which can recur locally and occasionally metastatize
- Pigmented schwannoma, to be distinguished from the above.

The fact that solitary schwannoma can exceptionally undergo malignant transformation, usually in the form of epithelioid MPNST but sometimes acquiring the features of a conventional or epithelioid angiosarcoma.

The description or rediscovery of several more or less distinct variants of neurofibroma, including:
- Pigmented (melanotic) neurofibroma, a neoplasm which can be confused with Bednar tumor (pigmented dermatofibrosarcoma protuberans); 30
- Dendritic cell neurofibroma with pseudorosettes, a controversial entity which some authors regard as being of melanocytic nature 31
- Neurofibroma with a skeletal muscle component (benign Triton tumor or neuromuscular hamartoma) 32

- The discovery that type I neurofibromatosis is due to a functional loss of NF1, a gene located near the centromere of chromosome 1733 and which encodes an ubiquitous protein known as neurofibromin, which is necessary for the correct negative regulation of ras proteins. 34 It has been shown that the tumors developing in this syndrome require a loss of NF1 in the cells destined to become neoplastic, as well as heterozygosity in the non neoplastic cells.

- The discovery that type II (central) neurofibromatosis is genetically different from type I, resulting from an alteration of the NF2 tumor suppressor gene, located in chromosome 2235,36

- The ultrastructural and immunohistochemical definition of the perineurial cell as the third essential component of the peripheral nerve sheath, together with schwann cells and fibroblasts. Immunohistochemically, this cell is positive for epithelial membrane antigen (EMA), claudin-1 and GLUT-137

- The description of a variety of neoplasms composed of perineurial cells, i.e., perineuriomas, including:
  - Cutaneous perineurioma (often misdiagnosed as epithelioid histiocytoma)38
  - Reticular and plexiform perineurioma (to be distinguished from myoepithelial tumors, extraskeletal myxoid chondrosarcoma, and myxoid synovial sarcoma39,40
  - Atypical perineurioma, containing scattered pleomorphic cells akin to those sometimes seen in ancient schwannoma and atypical (bizarre) neurofibroma41
  - Intraneural perineurioma42
  - Sclerosing perineurioma43
  - Granular cell perineurioma44

- The identification of cases of hybrid schwannoma–perineurioma (including the retiform variant of the latter) and neurofibroma-perineurioma.46

- The proposal that some small polypoid lesions of the colon composed of bland-looking spindle cells and initially named fibroblastic polyps might be either of schwannian (S-100 protein-positive) or perineural (EMA-positive) derivation. 47,48 These clinically insignificant lesions are not associated with type I neurofibromatosis or other inherited syndromes.

- The realization that a subset for soft tissue sarcomas previously included in other categories (such as liposarcoma or so-called MFH) are probably malignant perineuriomas 49

- A detailed description of the cytoarchitectural criteria for the diagnosis of MPNST. 50

- The remarkably wide spectrum of “divergent differentiation” that MPNSTs can exhibit, including skeletal muscle (“Triton tumor”), bone, cartilage, and blood vessels. 51,52

- The characterization of the epithelioid and glandular variants of MPNST. 53
• The identification of the plexiform variant of MPNST, a tumor that predilects children and adolescents and which is associated with an excellent prognosis, to the point of being regarded as benign by some authors.

• The description of palisaded encapsulated neuroma (also known as solitary circumscribed neuroma), a small, solitary benign papule of skin, often located in the face. Microscopically, it is characterized by a proliferation of schwann cells and numerous axons surrounded by a capsule derived from the perineurium.

• The continuing controversy as to whether neurothekoma, nerve sheath myxoma and melanocytic lesions of skin (particularly Masson’s neuronevus) should be regarded tumors of the peripheral nervous system or not.

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