The Potential Histogenic Relationship of the Peripheral Nerve to Synovioma

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Abstract

The belief that synoviomas differentiate from the synovial membrane has been widely accepted. Absolute proof is lacking, mainly because precancerous synovial atypia has not been documented in human tissue. During the last 50 years, pain has emerged as one of the significant features of synovioma, occurring very early in the course of the disease in some patients. Gross relationship to nerve, cumulative histological data, and theoretical relationships with three other cancers of neural origin suggest the nerve sheath as an alternate parent tissue for synovioma. All three cases illustrating nerve involvement are included.

Introduction: Problems in Analysis

The histogenesis of synovial sarcoma from synovium has been widely accepted, although exact documentation seems just beyond reach. One of the significant problems in histogenetic studies of this cancer is the fact that a variety of soft tissues constitutes the tumor bed. This spectrum is much less advantageous for determining the cells of origin than is a monomorphic background such as cartilage or notochord. In this situation, origin from undifferentiated mesenchyme with synovioblastic potential is a reasonable possibility (17). Another important problem in histogenesis is the fact that all human tumors, to our knowledge, have been relatively large when first diagnosed. Large size alone tends to obliterate histogenetic clues such as precancerous atypia and contiguous in situ changes. In this regard, our report of a minute synovioma detected because of tenderness in the absence of a palpable mass in a 34-year-old male is of interest (13). The tumor approximated 4.3 cm and contained nonmyelinated nerves. This finding, together with pertinent data collected by others, suggests that the relationship between nerve tissue and synovioma should be further explored.

Nerves and Pain in Synoviomas of Various Sizes

The detection of nonmyelinated nerves within this synovioma (13) was facilitated by the small volume of the tumor and has not to our knowledge been reported previously. The presence of these nerves offers a reasonable explanation for the prolonged tenderness experienced by this patient and also voices the more controversial possibility that nerves play some role in the induction phase of synovioma or that nerves or perineural mesenchyme may be the parent tissue of synoviomas. Some support for this hypothesis was provided by the report of Pack and Ariel (18) on a group of 11 patients with synovioma who presented with pain or tenderness prior to the appearance of tumor or swelling. The microscopic synovioma that we have reported (13) was capable of producing tenderness almost from its inception. Symptoms occurring prior to the emergence of a palpable tumor, referred to for convenience as the pretumor stage, have been amply confirmed by DeSanto et al. (7), Lohr (15), Coley and Pierson (6), Haagensen and Stout (11), Cadman et al. (5), and Thompson et al. (21). This nonpalpable phase may well hold the key to further assessment of the histogenesis of synovioma, since it is in the earlier stages of development that a tumor is most likely to retain identifiable parent tissue showing in situ atypia. Synoviomas have been found in gross continuity with: the brachial plexus (Lohr (15); Batsakis (2); and Pack, Case 17 (18)); the perineal nerve (DeSanto, Case 15 (7)); the internal popliteal nerve (Haagensen, Case 1 (11)); the radial nerve (Haagensen, Case 2 (11)); and probably the peroneal nerve (Coley, Case 4 (6)).

Apparent Histological Similarity between Synoviomas and Nerve Tumors

Zippel noted myxomatous changes in synoviomas of his patients, Patients 1 and 2 (23). The histochemical nature of mucin found in synoviomas is accounted for by Roth et al. (19). They found hyaluronidase-sensitive mucoid material in stroma outside the pseudoglandular spaces in their group of neck synoviomas. Identical conclusions were reached in a recent study of cutaneous metastases of synovial sarcoma (1). Myxomatous changes were present in the peripheral part of the microscopic tumor in continuity with small nerves. This change is also commonly found in solitary neurofibromas, and the suggestion that interstitial mucin is neural in origin is reflecting limited neural differentiation within the synovioma comes to mind. When histogenetic considerations are further extended, the role of endoneurium in the formation of nerve sheath myxoma may be important with reference to intercellular secretion as well as to embryological relationships to the meninges. The presence of psammoma bodies in the latter and in meningiomas is a familiar finding. Their concentric nature is strikingly similar to that of the calciospherites found in about 40% of synoviomas.

A further line of support for some relationship of nerve tissue to synovioma comes from 3 rare tumors which themselves have not been clearly defined: clear cell sarcomas of tendon sheath and aponeuroses; medulloepitheliomas of peripheral nerve; and neurid tumors of infancy. Regardless of their somewhat uncertain status, they retain what is believed to be a valid thread of continuity for histogenetic considerations. The clear cell sarcoma of tendon sheath and aponeuroses is a cancer of the extremities recognized and documented by Enzinger (9). He considered the cancer as a possible variant of synovioma.
Recentl, melanin granules have been found in the tumor and confirmed by ultrastructural analysis by 3 different workers (3, 12, 16), constituting a critical histogenetic clue. If the assumption that clear cell sarcoma is really a variant of synovioma stands the test of time, then it follows that the relationship of synovioma to the neural crest is quite intimate. Somewhat related are the occasional neural crest cancer which has a sarcomatous cartilage component (22) and the fact that the neural crest normally gives rise to mesenchymal structures (4), both being presumptive correlates to the nonepithelial component of synovioma. Medullopithelioiomas are controversial for another reason. They have an acceptable biphasic pattern and can have rather well-developed high columnar secretory epithelium quite closely resembling the well-differentiated synovioma. Their rarity, the resultant lack of tissue available for analysis by modern tissue technique, and the lack of familiarity with their morphological features provide some reason for making medullopithelioioma difficult to accept as an entity. The lesion reported by Lanford and Cohn (14), a large tumor mass (6.25 cm), was contiguous with the medial nerve, recurred to 2 x 2 cm in 4 months, and recurred a second time to 11 x 8 cm about 6 months after the first operation. The recurrence pattern has a similarity to the natural history of many synoviomas. Its histology is clearly biphasic (Fig. 1A). The epithelioid and glandular schwannomas may also have a similar relation to synoviomas. Also, the unusual neuroid congenital cutaneous tumor reported by DeMoragas and Sarro (8) was characterized by multiple polygonal pigmented cutaneous lesions which lost their pigment, became ulcerated, and finally resulted in the death of the infant at 8 months by tumor hemorrhage. The tumor contained a remarkable histological melange of neoplastic types, including melanoma, synovia, neuroid structures, and melanotic progonoma. In this light, the occasional synovia reported as having a pattern simulating rosettes of neurogenous origin (20) may constitute further supportive evidence (Fig. 1B).

Illustrative Cases

Case 1. The patient was a 34-year-old male who had severe localized tenderness for 18 months in the right upper thigh. No palpable mass, signs of inflammation, or history of previous trauma was found. A neurosurgeon suggested that the lateral femoral cutaneous nerve be "released." A second neurosurgeon used local anesthetics to give temporary relief. When the possibility of a glomus tumor was entertained, the area was "released." The osteotomy was performed, preserving the capsule. The tumor did not invade the muscle, nerve or bone. The nerve of the brachial plexus passed through the tumor, and lesions which lost their pigment, became ulcerated, and finally resulted in the death of the infant at 8 months by tumor hemorrhage. The tumor contained a remarkable histological melange of neoplastic types, including melanoma, synovia, neuroid structures, and melanotic progonoma. In this light, the occasional synovia reported as having a pattern simulating rosettes of neurogenous origin (20) may constitute further supportive evidence (Fig. 1B).

Case 2. The patient was a 70-year-old female with a tender mass on the medial aspect of the left os calcis simulating a ganglion. It measured approximately 2.2 cm in its largest dimension, had been present for at least 3 months, was quite painful on palpation, and was movable s.c. On dissection, the tumor was infiltrating fat irregularly and was not well circumscribed. Histologically, the tumor also infiltrated fascia and was interpreted as a synovial sarcoma, epithelioid type. It was dominated by a fairly uniform spindle cell population, had endothelioid spaces such as seen in Case 1, and also had focal interstitial areas of myxoid differentiation. Small unmyelinated nerves were found within its interior and blended with spindle cell tumor stroma. A large neighboring nerve showed prominent atypical proliferation of Schwann cells (Figs. 2, 3 and 4). The operative site was reexcised more extensively, and the patient was well 13 months postoperatively. She had a history of successful radical right mastectomy for carcinoma 10 years prior to the present operation.

Case 3. The patient was a 35-year-old male with a palpable mass in the left axilla approximating a "small- to medium-sized lemon." The tumor gave pain and numbness for 18 months, mainly in the distribution of the ulnar nerve. At surgery, a large nerve of the brachial plexus passed through the tumor, and several other branches were draped across the exterior surface of the tumor. Approximately two-thirds of the tumor was removed, preserving the capsule. The tumor did not invade the vascular structures and appeared grossly benign. However, permanent sections documented synovial sarcoma with calcospherites, multifocal myxoid areas, and cellular epithelioid areas margined by spindle cell fascicles. No glandular structures were found. Nonmyelinated nerves were found within the interior of the tumor (Fig. 5) and seemed to blend with adjoining spindle cells of the cancer. The patient had more extensive surgery but expired approximately 16 months after the first operation.

Concluding Remarks

The belief that synovia differentiates from synovial membrane has become firmly entrenched. However, on critical analysis, it is apparent that definitive proof has been lacking. No evidence of in situ synovial membrane atypia has been found in surgical or autopsy specimens, although experimentally induced synovial atypia has been alluded to (1). Further, the cancer develops regularly outside of the synovial structures. While we have come to accept this as one of the peculiarities of the cancer, it is a prominent deviation from current concepts for a cancer to arise away from its "parent" tissue. The well-documented ectopic synoviomas of the abdominal wall, the brachial plexus, and even the tonsillar fossa further illustrate this histogenetic discrepancy.

On the other hand, the proposition that synovia originates from nerves is proposed with a large measure of caution. While the smallest reported synovia (13) clearly contains nerves, the presence of the latter does not necessarily prove that the nerves gave rise to the tumor. In fact, no one feature favoring nerve relationship (e.g., high frequency of pain, occasional myxoid character, calcospherites resembling psammoma bodies, and the relation of the tumor to clear cell sarcoma, peripheral nerve medulloepithelioma, and neuroid tumors of infancy) can be considered definitive. Nevertheless, when these isolated facts are viewed together, they seem to give credence sufficient enough to further explore the proposition that synovia may be neural in origin.
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References


Fig. 1. In A, the biphasic pattern of this medulloepithelioma of the right arm includes well-delineated epithelial spaces. Reprinted from Ref. 14 with permission of the publishers and Dr. I. Cohn. In B, this synovioma of the right knee had rosettes, raising an initial strong suspicion of a neuroblastoma. Reprinted from Ref. 20 with permission of the publishers (authors deceased).

Fig. 2. The synovioma shows an endothelioid pattern with calcospherites, clefts, and some fascial remnants in the lower left corner (Case 1). H & E, x 39. Left inset, nerves contained within a myxoid fascicle forming the periphery of the tumor. H & E, x 100. Right inset, small nonmyelinated nerves within the interior of the tumor showing well-delineated axons. Bodian, x 570.

Fig. 3. An altered hypercellular nerve is present at bottom center situated at the edge of the tumor which extends from the left to the lower right corner, involving fascia (Case 2). Arrows, area enlarged in Fig. 4. H & E, x 46. Inset, a similarly altered nerve in the interior of the tumor H & E, x 285.

Fig. 4. An enlargement of an area marked by arrows in Fig. 3 shows atypical Schwann cells having a concentric pattern of fibrillar hyperplasia. (Case 2). H & E, x 460. Inset, further enlargement of center focus marked by parallel lines. H & E, x 1140.

Fig. 5. The synovial sarcoma exhibits a prominent aggregate of calcospherites in the right upper corner (Case 3). A diagonally oriented unmyelinated nerve is present to the left of the lower central region. H & E, x 168.
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