Neuroendocrine (Merkel Cell) Carcinoma in Regional Lymph Nodes without Primary Site

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Neuroendocrine carcinoma of the skin was described by Toker in 1972 as trabecular carcinoma [1]. Although the entity is widely known as Merkel cell carcinoma because of its ultrastructural similarity to the normal Merkel cell, the term neuroendocrine carcinoma of the skin is more appropriate because of the histologic and histochemical features of the malignant cells. Many hundreds of cases have been described in the literature but the biological behavior and treatment of this aggressive tumor have not been precisely defined. NCS tends to metastasize to regional lymph nodes and to spread hematogenously to other organs, primarily liver and bone. Moreover, the appearance of NCS in regional lymph nodes without an apparent primary site has been reported only rarely [2–4]. This report adds another two cases to the 13 documented in the literature.

Patient Descriptions

Patient 1

A 59 year old male atomic reactor technician presented with a painless lump in his right groin of 2 weeks duration. Physical and routine blood tests were normal. Meticulous physical examination did not reveal any suspicious skin lesions and no known skin lesion had been removed previously. Fine needle aspiration examination showed malignant cells; excisional biopsy was therefore performed, which revealed NCS by immunohistochemical stains and electron microscope. Extensive imaging work-up did not show any residual disease or metastasis. The patient refused radical inguinal lymph node dissection and was treated with radiation to a total dose of 65 Cy. Eight months later the patient developed a progressive debilitating neurologic syndrome that included paraparesis, vertigo, vertical diplopia and paresthesia. Since an exhaustive neurologic work-up did not reveal the etiology, a local recurrence was detected on computed tomography scan. Surgical resection was undertaken, followed by chemotherapy with cytoxan, methotrexate and 5-flurouracil. There was minor improvement in the apparent paraneoplastic syndrome, but the patient died of pulmonary complications without known metastatic disease.

Patient 2

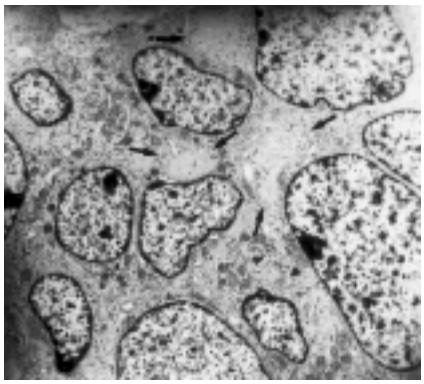
A 69 year old man with known prostate carcinoma was found on routine examination to have a 3 cm mass in his left groin. After fine needle cytology suggested lymphoma an excisional biopsy was performed, which revealed NCS. Imaging work-up suggested additional evidence of involved local lymph nodes but no distant metastasis. Physical examination did not find any skin lesions. The patient was treated with three cycles of cytoxan, methotrexate and 5-flurouracil at another institute without response, after which he underwent radical inguinal lymph node dissection. Metastases were detected in three additional nodes and adjuvant radiation therapy was administered. One and a half years later the patient developed severe abdominal pain. Gastroscopy detected a gastric polyp in the cardia. The polyp was excised and diagnosed histopathologicaly to be a Merkel cell carcinoma metastasis. A CT scan around that time found infiltration of small bowel mesentry and retroperitoneal lymph nodes. He was treated with cisplatinum and VP-16, but he died shortly after, 2 years following the initial diagnosis.

Pathology

• *Macroscopy.* In each case there was a single unfixed lymph node that measured 1.2 to 3 cm in its longest diameter. On cut sections, the lymph nodes showed white-pink tissue and a nodular pattern. In patient 1, large areas of necrosis were seen as well. Some sections were fixed in formalin, others in B5 solution and then embedded in paraffin. The 5 μ thick sections were stained routinely with hematoxylin-eosin.

• *Light microscopy:* The two cases showed similar histologic features. The lymph nodes were invaded by tumor cell masses with organoid and trabecular patterns. The cells were fairly uniform in size, round to oval. The cytoplasm was scanty and poorly defined. The nuclei showed a finely granular chromatin pattern and a well-defined indented nuclear membrane. The nucleoli were small and usually close to the nuclear

NCS = neuroendocrine carcinoma of the skin



Ultrastructurally the cells in both patients showed oval nuclei with granular chromatin and small nucleoli close to the nuclear membrane. "Paranuclear dots" (arrows) are evident near the nuclei. (Electron microscopy x 4,500)

membrane. Fragmented nuclei (apoptosis) and numerous mitoses were present in both cases. Melanin pigment was absent.

• *Electron microscopy*: In both cases tissue fragments were obtained for ultrastructural study. The fragments were fixed in Kamowsky fixative, then in 1% osmium tetroxide and embedded in araldite. Tumoral areas were selected by observation of semithin sections, stained with methylene blue + Azur II + Basic Fucsin. Ultra-thin sections were routinely stained with uranil acetate and lead citrate and examined with a Philips KM 200 electron microscope. The electron microscope studies showed that the cells had roughly spherical, polygonal or indented nucleii [Figure], scanty cytoplasm with numerous mitochondria and round-shaped neurosecretory granules showing the characteristic homogeneous electro-dense core and peripheral halo. We did not find any spherical or elliptical melanosomes showing the typical concentric lamellar periodicity. Intermediate filaments were present sparsely in the cytoplasm and numerous cells showed packed perinuclear intermediate filaments. This distinct pattern is known as "paranuclear dots" (arrows). This pattern is very characteristic of Merkel cells.

• *Imunohistochemistry*: Sections from the tumors were submitted for immunohistochemical stains including: S-100, HMB-45, low molecular weight keratin, neurofilament, synaptophysin and chromogranin. Low molecular weight keratin and neurofilaments were positive in the distinct "paranuclear dots" pattern. Synoptophysin and chromogranin showed more diffuse cytoplasmic positivity. S-100 and HMB-45 were negative in the tumoral cells, excluding the possibility of metastatic melanoma.

LMW =

Comment

The two cases reported here of Merkel cell carcinoma within lymph nodes with no apparent primary site are added to the 13 cases already documented in the literature [2–4]. This rare entity is controversial since Merkel cell carcinoma in a lymph node can be difficult to differentiate histopathologically from other poorly differentiated small cell or neuroendocrine carcinomas or metastatic melanoma. However the "paranuclear dots" phenomenon represents a characteristic feature for Merkel cell, found only exceptionally in small cell carcinomas of internal organs. The paranuclear dots represent a paranuclear tangle of intermediate filaments that are a mixture of keratin and neurofilaments, as demonstrated by immunohistochemical stains. The consistent immunoreactivity for neurofilaments and keratin in the "paranuclear dots" pattern in Merkel cell is useful in the differential diagnosis of small cell carcinomas of lung or carcinoma in other organs where this feature is usually absent.

Concerning the differential diagnosis of metastatic malignant melanoma, the negativity for immunoperoxidase stains like S-100 and HMB-45, together with the electron microscope studies, help to exclude this possibility. Thus the reported cases fulfil firm histopathologic criteria for Meckel cell tumor. There are two possible explanations for this phenomenon. First, the small primary lesion conceivably regressed before the clinical appearance of metastasis, or the lymph node was the primary site, occurring in precursor cells. A few cases of spontaneous regression of Merkel cell tumors have been reported [5], interestingly enough only in women. The second hypothesis, proposed by Eusubi et al. [2], assumes that primitive stem cells within lymph nodes represent the precursor cells for the tumor. This theory is problematic since Merkel cells or their precursors have never been identified within lymph nodes.

The rarity of this phenomenon makes it very difficult to set standards for treatment. Surgery remains the mainstay of therapy of course, with radical regional lymph node dissection indicated. Despite the known limited effectiveness of chemotherapy in this disease, no series of adjuvant therapy following surgical extirpation has been reported. Adjuvant radiation therapy has been utilized for local control of primary tumors, but its use in regional disease has not been determined. In fact it failed to control regional disease in our first patient, which led to an apparent bizarre paraneoplastic syndrome. In conclusion, the entity of Merkel cell carcinoma presenting in regional lymph nodes is extremely rare. Aggressive surgical treatment seems indicated, and adjuvant chemotherapy can be considered on an individual basis. Advances in molecular biology may shed some light on the ongoing dilemma of the precursor cell. Establishing an international registry of cases would be helpful in understanding the natural history of this phenomenon.

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