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Neuroepithelioma (Neuroblastoma) Arising in an Adult
A Case Report

J. Verwey [1], R. Slater [2], W. Kamphorst [3], and H. M. Pinedo [1]

[1] Department of Oncology, Free University Hospital, Amsterdam
[2] Institute of Human Genetics, University of Amsterdam
[3] Department of Pathology, Free University Hospital, Amsterdam

Summary. Cytogenetic studies on neuroblastomas arising in children have revealed consistent abnormalities of the short arm of chromosome number 1. Partly because of the rare occurence of neuroblastomas in adults, extensive cytogenetic studies in this group of patients have not been performed. We report a case of a neuroepithelioma (neuroblastoma) arising in a 50-year-old male patient. On chromosome analysis of a metastasis, a stemline with karyotype 47,XY, + der1(1 qter---1 cen::1q21---1 qter) was identified. The possible consequences of this result and those of results previously reported in the literature are discussed.

Key words: Neuroblastoma – Chromosome analysis

Introduction

Neuroblastoma is a malignant tumor of neural crest origin, that may arise at any location containing sympathetic tissue, and along peripheral nerves.

In fact, primitive neuroectodermal tumors with rosettes, arising in association with peripheral nerves, have been occasionally reported and classified as ependymoma, medulloepithelioma, medulloblastoma and peripheral neuroephithelioma (peripheral neuroblastoma) [5, 20, 21–23, 28, 29, 34].

Several authors have questioned these separate classifications and suggest that these tumors represent neuroblastomas arising in association with peripheral nerves [5, 21, 26].

Although neuroblastoma is predominantly a disease of childhood, the tumor can also occur in adults [13, 25, 26]. Studies on tumors as well as cell lines have recently identified three cytogenetic abnormalities of neuroblastoma: (1) structural aberrations involving the short arm of chromosome 1 [3, 9, 11, 17, 18], (2) the presence of double minutes (DM), and (3) the presence of homogeneously staining regions (HSR). Both DM and HSR however, have also been reported for other malignancies [24, 33]. Up until the present time, cytogenetic studies have all been done on samples derived from classical neuroblastomas in children. We report a case of a neuroepithelioma in an adult.

Offprint requests to: J. Verwey, Department of Oncology, Dr. Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

Methods

A 50-year-old man, was found to have a tumor arising from the right tibial nerve, which after apparently radical surgery was identified as being a neuroepithelioma (neuroblastoma). Screening for metastases was negative and the patient received postoperative irradiation up to a dose of 5,000 rad. However, 3 months later, in August 1983, retroperitoneal and pulmonary deposits were discovered, and the patient started treatment with cyclophosphamide, vincristine, doxorubicin, and DTIC (CYVADIC). The pulmonary deposits disappeared and the retroperitoneal metastases steadily regressed during the first two treatment courses, but stabilized during the following two. It was decided to try to convert the remission into a complete one by additional surgery. At operation in November 1983 a large retroperitoneal tumor was found that could not be radically resected. The tumor was biopsed extensively. After operation it was planned to give another two cycles of CYVADIC, followed by abdominal irradiation. However, after another cycle of CYVADIC progression was noted in February 1984. Treatment was changed to cisplatin plus VM-26 and the patient again achieved a partial remission. He ultimately died of tumor progression shortly after.

For cytogenetic studies, a sample of the tumor was placed in sterile physiological saline immediately after removal from the patient. The tissue was then minced finely in RPMI 1,640 containing 15% fetal calf serum, 1-glutamine and antibiotics. Part of the resulting cell suspension was used for a short-term culture and the remainder plus any tissue fragments were incubated overnight at 37 °C in tissue culture medium containing 1 mg/ml collagenase II (Worthington Diagnostic Systems Inc., Free Hold, NJ, USA) and 20 μg/ml DNase I (Sigma Chemical Company, St. Louis, MO, USA). This mixture was then pipetted to break up any remaining fragments, centrifuged, and resuspended in fresh medium. These cells were used to set up a cell line in tissue culture.

Chromosomes were obtained from the short-term culture after 24 and 48 h by adding colcemid (final concentration 0.02 µg/ml) for 1 h. Metaphase preparations were obtained from the cell line by adding colcemid (final concentration 0.1 µg/ml) for 20 min. Cytogenetic analyses was performed using QFA followed by CGB staining techniques according to the International System for Human Cytogenetic Nomenclature [1].

Results

Pathology

The tumor resected from the right tibial nerve was crowded with small cells with negligible cytoplasm and round or oval highly hematoxyphilic nuclei. Limited areas showed Homer Wright rosettes (Fig. 1), and mitotic figures were frequent. The tumor was traversed by a few relatively normal nerve fascicles (Fig. 2) and surrounded by a collagenous capsule. The Bodian, Bielschowski, and Grimelius staining methods revealed no neurofibrils and argyrophil granules, respectively.

In the biopsy from the retroperitoneal mass densely packed tumor cells were seen to infiltrate the adipose and lymphoid tissue. The nuclei were often arranged in globules in a fine fibrillar eosinophilic background with a glial quality. Rosettes were missing, and mitotic activity was considerable. Bodian, Bielschow-

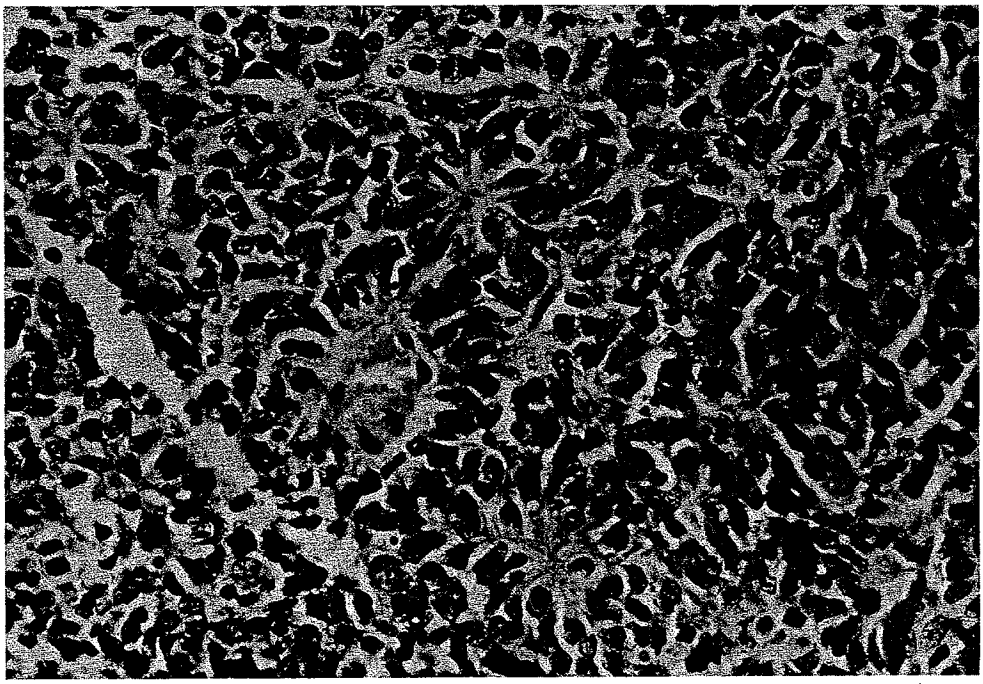

Fig. 1. Primary tumor, showing Homer Wright rosettes

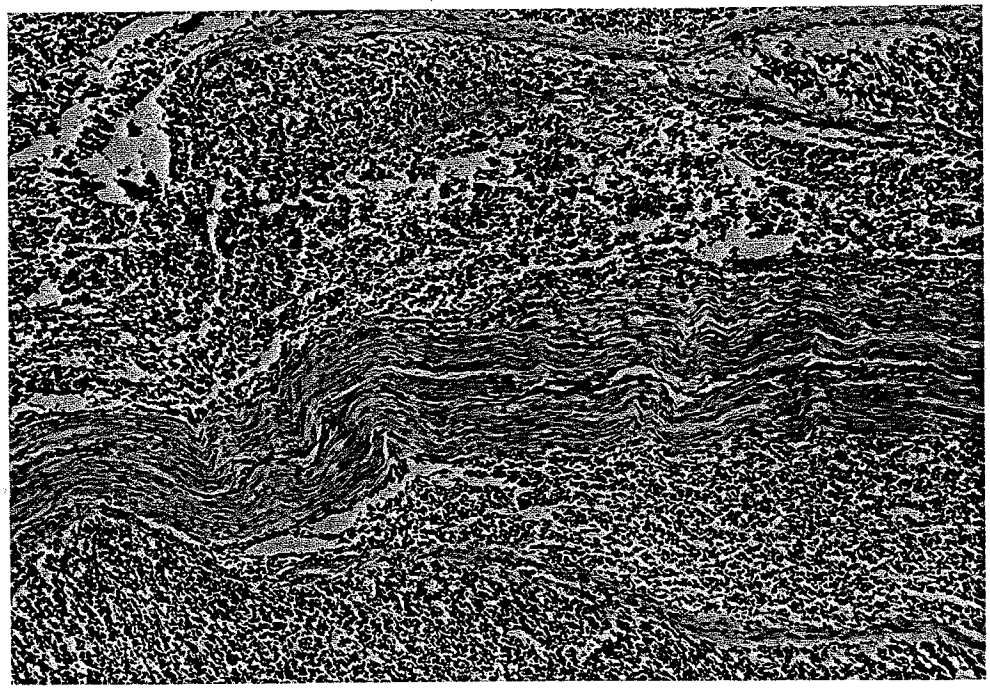

Fig. 2. Primary tumor, traversed by peripheral nerve fascicles

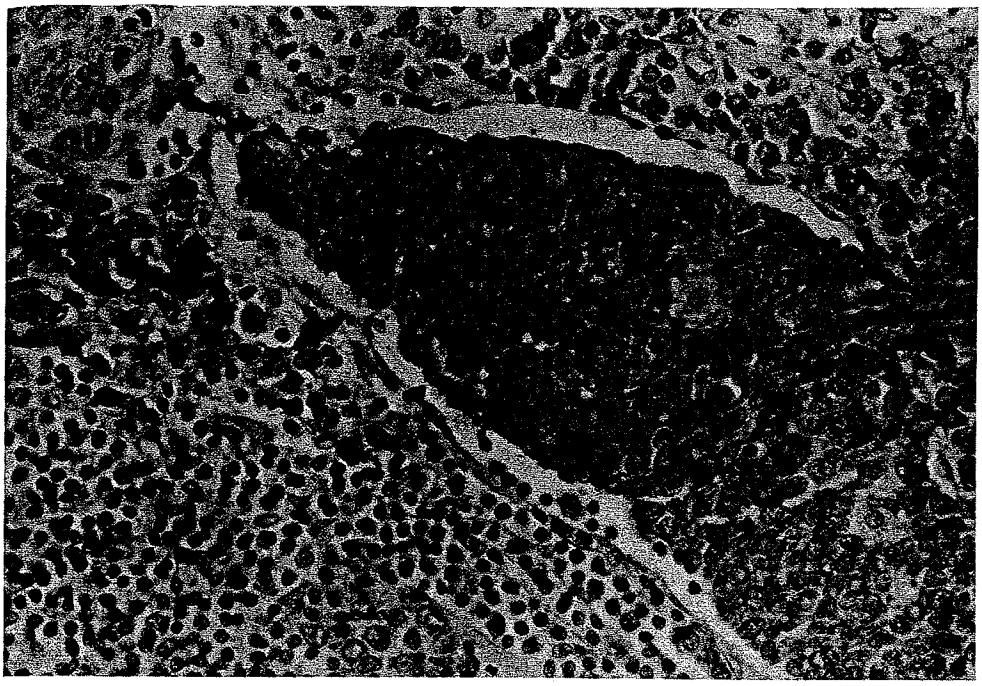

Fig. 3. Lymph node metastasis; tumor cells reacting positive for NSE (NSE-PAP, counterstained with hematoxylin)

Fig. 4. Q-banded karyotype of the neuroblastoma after short-term tissue culture: 47,XY,+der1(1qter---1 cen::1q21---1qter),11q+; inset shows the normal chromosome number 1 and the marker chromosome 1 after sequential C-banding

ski, and Grimelius stains were negative. Yellow granules dispersed in the tumor showed a positive reaction for iron and stained negative for melanin (Fontana-Masson).

PAS and PAS diastase stains revealed no glycogen. Reticulin fibers divided the tumor mass into islands but were missing between individual cells.

Immunostaining with the indirect PAP method for neurofilaments, glial filaments and S-100 protein was negative.

Immunostaining for neuron-specific enolase (NSE) showed a strong cytoplasmic reaction of isolated cells and cell groups (Fig. 3). Ultrastructural study revealed cells with ovoid nuclei with an occasional cleft, evenly spread chromatin, and a small amount of cytoplasm containing a moderate amount of mitochondria, polyribosomes, a scanty rough endoplasmic reticulum and very few dense core vesicles. There were few cell processes, sometimes with microfilaments. Macula adherens type of junctional com-

plexes were frequent. A small amount of basal lamina-like material was sometimes present in the extracellular spaces.

Cytogenetic studies

Short-therm culture. A total of 30 metaphases were analysed. All were in the diploid range except for a single polyploid cell. The chromosome number ranged from 41-47 with a mode at 47. A stemline was identified with the following karyotype 47,XY,+ der1(1qter---1cen::1q21---1qter). This marker chromosome was present in all metaphases except 3 where the only abnormality again involved number 1 with a duplication of region 1q12---1q32 in one homologue (1pter---1q32::1q12---1qter). Single instances of other markers (7p+, 7q+, 11q+) were found in cells with the extra derivative number 1 (Fig. 4). Four cells with a normal karyotype were identified.

Cell line. Chromosome analysis at the fifth passage in tissue culture revealed a normal male karyotype.

Discussion

The reported patient had a neuroepithelioma (neuroblastoma) arising in a tibial nerve. Since the first description of a primitive neuroectodermal tumor with rosettes, arising in association with a peripheral nerve [34], such tumors have been reported occasionally and have been designated as ependymoma, neuroepithelioma, medulloepithelioma, medulloblastoma and primitive neuroectodermal tumor (neuroblastoma) of a peripheral nerve [5, 20–22, 29, 30]. Harkin and Reed [19] have suggested that these tumors may be primary neuroblastomas and they questioned their separate classification. Bolen et al. [5] stated that cell culture techniques and ultrastructural studies have convincingly demonstrated that they represent neuroblastomas arising in association with peripheral nerves. Hashimoto [21] found only 2 of 15 cases of malignant neuroepithelioma discernibly related to peripheral nerves, while Mackay [26] found 2 out of 9 neuroblastomas to be possibly related to small peripheral nerves. These data suggest the close relationship of neuroepitheliomas to the group of neuroblastomas.

Neuroblastoma, although predominantly a disease of childhood, also occurs in adults [3, 9, 11, 13, 17, 18, 25, 26]. Recent studies have reported over 40 adult patients, aged 17–75 years, diagnosed as neuroblastoma or neuroepithelioma. Although there appears to be a trend for neuroblastoma to have a worse prognosis with increasing age in children [6, 14], a less aggressive biologic behavior of the neoplasm in adults has been suggested [13, 26]. Moreover, the experience that out of 13 adult patients with advanced disease and treated with chemotherapy, 8 responded (2 complete and 6 partial remissions), indicates that metastatic neuroblastoma in adults can be treated quite effectively with chemotherapy. It has been reported that chemotherapy may induce maturation of the tumor in adults [25], while well-documented cases of spontaneous maturation are also known [15, 31].

The diagnosis of neuroblastoma by light microscopy can be difficult because of similarities between the lymphocyte-like neuroblastoma cells and cells of other round cell neoplasms [26]. Electron microscopy may be an aid to the diagnosis, revealing distinctive changes such as peripheral dendritic processes containing membrane-bound granules and longitudinally oriented microtubules within their cytoplasm [21, 26]. Also immunohistochemically, a mainly positive reaction for NSE may be helpful in distinguishing neuroblastomas if rosettes are absent [21].

Cytogenetic studies after short-term tissue culture of a sample derived from the tumor of the reported patient revealed the presence of an abnormal stemline with the karyotype 47,XY,+der1 (1qter---1cen::1q21---1qter). This near diploid chromosome number is a common finding in neuroblastoma, although instances of near triploid and near tetraploid cases have been reported [8–10]. Chromosomal banding analysis which up until now has always been performed on samples derived from childhood neuroblastomas, has shown the most consistent abnormality to be loss or rearrangement of the short arm of chromosome number 1 (3, 4, 9, 11, 17, 18]. The most frequent break point appears to be 1p32 with all rearrangements and deletions involving material distal to 1p31, always including 1p34 to 1pter [9, 17]. Such variation was not found in the present study. This may reflect the peripheral origin, although other neuroblastomas without changes in 1p have also been reported [17]. If the loss of activity of one or more genes in this region is a prerequisite for tumorigenesis in neuroblastoma this could take the form of a submicroscopic point mutation, or visible loss, or rearrangement in chromosomal material. It is of particular interest that the gene for the beta-subunit of the human nerve growth factor, a polypeptide involved in the regulation of growth and differentiation of sympathetic and certain sensory neurons, has been assigned to the short arm of chromosome 1 (1p22), as has the N-ras proto-oncogene [4, 12, 16]; and in addition the transforming gene Blym-1 is located in band 1p32 [28].

Our patient had tetrasomy of region 1q21---1qter in the stemline and trisomy 1q12---1q32 in the remaining abnormal cells, demonstrating a strong selection pressure for duplication of the long arm of chromosome number 1, particularly region 1q21---1q32.

Trisomy 1q has also been observed in primary neuroblastoma and cell lines [4, 9]. Trisomy and tetrasomy of this region is well documented being found in both hematological disorders and solid tumors [32, 33]. In addition trisomy 1q has been observed as a secondary event in the evolution of karyotypic changes in both ovarian and hematological malignancies [2, 27]. This type of variation appears to be associated with the later stages of tumor development and it has been proposed that it plays a role in tumor progression [7, 32]. The patient in the present study had been diagnosed as having neuroepithelioma some time before the cytogenetic analysis was carried out and in addition had been treated. The observed chromosomal variation involving the long arm of chromosome 1 therefore in this instance also reflects the later stages of tumor development.

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