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Case Reports

Case reports are accepted under this heading. These reports should be short and concise and contain a minimum of figures, tables and references.

LACK OF N-MYC-AMPLIFICATION AND NORMAL KARYOTYPE IN STAGE IV-N NEUROBLASTOMA

The prognosis for children over one year of age with Evans stage IV neuroblastoma (NB) is poor (1–3). However, Rosen et al. (4) have recognized a small group of patients with stage IV neuroblastoma over the age of one year, who had spread only to lymph nodes and who had a relatively favorable prognosis. This entity was designated neuroblastoma stage IV-N.

We report a 10-year-old child with stage IVN-NB, who was treated with chemotherapy, surgery and myeloablative chemotherapy, followed by the autologous bone marrow transplantation (BMT). Five years from diagnosis, the child is alive with no evidence of disease.

Extensive laboratory investigation of this patient's tumor indicated that it was distinctly different from the usual findings in children with stage IV neuroblastoma. This unusual clinical presentation suggested that the unique pattern of metastases was consequent to aberrant expression of tumor homing receptors. We attempted to analyze this hypothesis by further delineation of the malignant cells by immunophenotyping.

Case report. A-10-year-old male presented in June 1989 with a visible left upper abdominal mass and lymphadenopathy in the cervical, inguinal and axillary nodes. Computerised tomography showed a retroperitoneal tumor measuring $10 \times 8 \times 6$ cm, with extension to the posterior mediastinum. No calcification was apparent on abdominal x-ray and CT examination. Chest x-ray and CT were normal. The tumor was clearly not resectable. Liver and bone scans were normal. Urinary VMA and HVA were within the normal range. Bone marrow biopsy and aspiration demonstrated no malignant cells, but a large population (35%) of very young lymphocytic cells, expressing CD19, HLA-DR and CD10 on their surface membrane was identified in the bone marrow. A biopsy of a supraclavicular node revealed infiltration by NB cells. The identity of these cells was proven by immunophenotyping studies showing that the infiltrating small round cells membrane stained positive with the monoclonal antibodies 1153 and UJ13A while the cell cytoskeleton was identified as neurofilament, all considered to be specific for NB (Figs. 1 and 2). The neighboring lymphocytes stained positively with CD3 (Fig. 3). Molecular studies showed no N-myc amplification, and karyotype examination of the disease tissue was normal (data not shown). An attempt to identify an aberrant expression of the lymphocyte homing receptor (LHR) by using NKI-P1 antibody on frozen section revealed no such expression by NB cells.

The patient was treated with four courses of chemotherapy, consisting of vincristine, cisplatin, cytoxan and VM-26. A dramatic clinical response was achieved with more than 50% reduction in the total tumor size. At this point the patient underwent surgical resection of the abdominal mass. The left adrenal tumor mass was removed and the left kidney was salvaged. However, surgical margins showed the presence of viable tumor cells. He therfore underwent bone marrow harvest followed by 10 Gy to the tumor bed in the abdomen, and an additional course of the CCG-323P2 protocol (vincristine, cyclophosphamide, cisplatin and VM-26). Thereafter he received myeloablative chemotherapy consisting of VP-16, cisplatin and melphalan plus 10 Gy to the whole body in three fractions, followed by an autologous BMT.

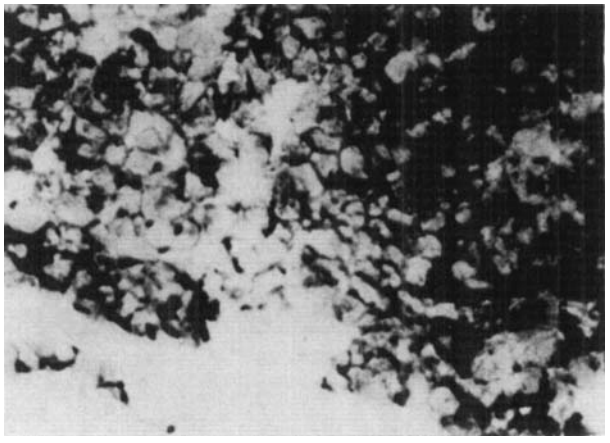

Fig. 1. Lymph node stained with monoclonal antibody to neurofilament protein with the AP-AAP technique.

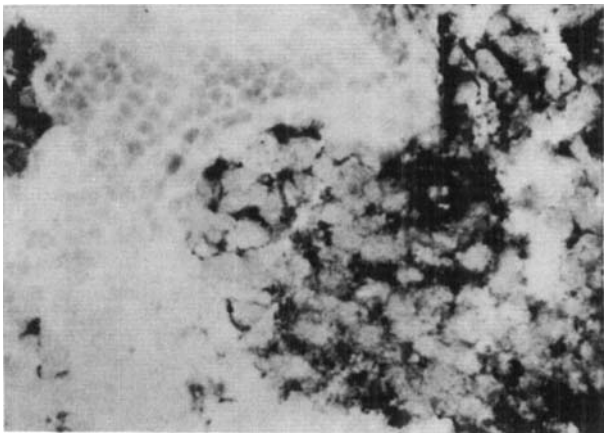

Fig. 2. Lymph node stained with monclonal antibody UJ13A with the AP-AAP technique.

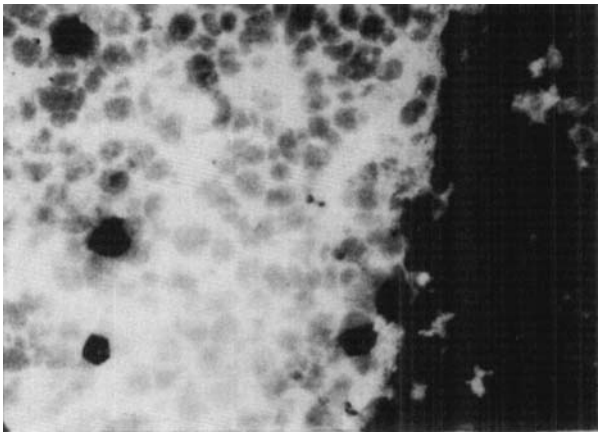

Fig. 3. Lymph node stained with monclonal antibody CD3 with the AP-AAP technique.

After BMT he received 6 weekly courses of 13-cis-retinoic acid at a dose of 125 mg/m^2/day which were well tolerated, except for mild dryness of the skin. Today, five years after diagnosis, he is alive with no clinical or radiological evidence of residual disease.

Discussion. Rosen et al. (4) described a small subgroup of IV-N NB whose prognosis was significantly improved compared to that

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of most stage IV patients older than one year at diagnosis. They reviewed the medical records of 118 children with NB, over a period of 10 years, 46 of them were older than 1 year of age with stage IV at diagnosis. Treatment protocols varied during this period. Six of the patients were classified as stage IV-N solely because of extensive lymph node involvement (cervical/axillary/thoracic/adbominal/pelvic) without metastasis to bone marrow, parenchymal organs or bones. The children were treated with either vincristine, doxorubicin, cyclophosphamide (VAM)-DTIC, or mustard, doxorubicin, cisplatin, DTIC, vincristine, cyclophosphamide (MADDOC). Three of these 6 patients (50%) were long-term disease-free survivors, compared with none of 40 patients with extra nodal metastatic disease ($p < 0.0002$). In these patients as in our patient there was a male preponderence and frequent localization of the primary tumor to the left upper abdomen. No molecular, immunological or chromosomal studies were performed on Rosen et al.'s cases. Since this clinical description we have not encountered additional reports of this entity. Their findings, however, are intriguing from both the clinical and basic standpoints, suggesting a possible mechanism for homing of tumor cells to specific target organism in general, and to the lymph nodes in NB in this particular case.

We present a case of a child with IV-N NB, who shared the clinical characteristics with the patients described by Rosen et al. This male patient presented with a primary tumor in the upper left abdomen and metastases confined to the lymph nodes. He was treated by an aggressive combined approach, consisting of chemotherapy, surgery, radiotherapy, and finally by myeloablative therapy followed by autologous BMT, and is now free of disease and in very good health.

Apart from the unusual spread of disease, the biology of this tumor was distinctly different from the usual presentation of stage IV NB. The pathology of this tumor according to Shimada classification (5), never revealed a nodular distribution of the malignant cells or mitotic karyorhectic index of over 100/5000. Urinary VMA and HVA were not elevated. No N-myc amplification was demonstrated in the involved lymph node or the primary tumor, nor were chromosomal abnormalities shown. Immunophenotyping of the BM cells did not reveal NB cell, while it did show an expanded CD10 positive lymphoblast population, both of which have been shown by others and ourselves to be associated with a favorable prognosis in advanced NB (6, 7). The nerve growth factor (NGF) receptor gene which was recently found to be a favorable predictor of prognosis, being expressed in the early stages of the disease (stage I, II, and IVS) (8), was not tested.

The hall mark of malignant neoplasms in their ability to spread beyond the site of origin and produce metastases in distinct organs. This non-random process depends on the interaction of specific tumor cells with a compatible milieu provided by a particular organ microenvironment; the molecular basis of which is recently becoming less obscure. Biological and molecular findings support the hypothesis that organ-derived, perhaps, organ-specific, paracrine growth factors stimulate the growth of receptive malignant cells that possess the appropriate receptors (9). Staroselski et al. (10) showed that clonal dominance is influenced by the organ environment in which the primary tumor grows (10).

Lymphocytes express cell surface molecules termed homing receptors that mediate their selective attachment to specialized high endothelial venules found within secondary lymphoid organs (11, 12). This mechanism has been implicated in the pathogenesis of metastatic disorders. Pals et al. (13), showed that the degree of expression of the LHR correlated with the extent of dissemination of tumors; so that increased expression was found in disseminated and decreased expression in localized disease. Kahn (14) reported that the adhesion molecule CD44 found normally on lymphocytes also is present on the surface of pancreatic tumor cells that are metastatic. Experimental evidence has also been presented showing that transfer of homing receptor genes by cell fusion resulted in transformation of non-metastatic to metastatic cells (15).

We suspected that the specific spread to lymph notes in this patient implicated a distinct homing mechanism. This hypothesis, unfortunately, could not be substantiated with the lymphocyte homing receptor antibody that we tested. However, it still seems conceivable to us that a distinct surface antigen of this particular tumor cell determined this pattern of spread.

The clinical course and favorable outcome in this patient support the observation by Rosen et al. that these patients who appear to have a poor prognosis from the outset in fact represents a unique entity with a more favorable prognosis and deserve an aggressive protocol aiming for cure. Rosen's favorable cases were quite successfully treated with conventional chemotherapy, but the presence of viable tumor cells in the tumor margins after the completion of the chemotherapeutic course was in our opinion a sufficient reason for BMT in this case. More research is needed to identify growth factors, cytokines, and homing receptors which may be involved in the preferred dissemination of tumor cells to lymph nodes.

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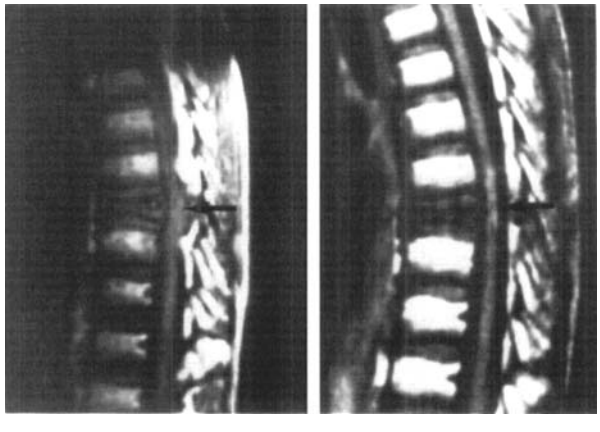
LONG-TERM RESPONSE TO RADIOTHERAPY OF VERTEBRAL HEMANGIOMA RESULTING IN PARAPLEGIA

Paraplegia caused by vertebral hemangiomas (VH) is infrequent. The most representative series published are those by Fox et al. (1), Glanzman et al. (2), Yang et al. (3), and Bergstrand et al. (4), including 59, 62, 23 and 13 cases respectively. In these patients, surgery and radiotherapy were used in combination or as single modalities. The recommended treatment (5–11) varies for the following reasons: 1) the number of patients treated are scarce, 2) the treatments are not uniform and 3) the results are obtained through treatment of a group of patients which are heterogenous in symptoms or in neurological deficits. The case of paraplegia as a result of VH presented below received radiotherapy and achieved a full immediate recovery which has now persisted for more than 5 years. The characteristics of radiotherapy as a singular modality treatment for patients with paraplegia are also discussed.

Case report. In 1989, a 12-year-old boy presented with severe back pain at the dorsal spine during periods of exercise. He was examined in our outpatient clinic, and complained of pain upon pressing the T8 vertebrae. A radiogram and a CT scan of the dorsal spine revealed a compressor fracture of the T8 vertebrae and 'coarse vertical striations', characteristics of VH. The pain disappeared after a few days of treatment with NAISDs. Vertebral hemangioma was diagnosed and the patient was followed without any other treatments. Sixteen months later, the patient was admitted for progressive motor weakness of both lower extremities which lasted for several days. The physical examination revealed paralysis of both extremities and a decrease of the Achilles and patellar reflexes, in addition to loss of sensation from T8 downward. A magnetic resonance (MR) scan was done, which revealed in sagittal T1 weighted image a hypointense lesion in the T8 vertebral body and an epidural intracanalicular lesion (Fig. 1a). In the T2 weighted image, the lesion was hyperintense. The treatment consisted of radiotherapy at a total dose of 37.5 Gy of ^{60}Co teletherapy in 20 fractions (daily). A post-treatment MR scan revealed disappearance of the intracanalicular lesion in the T1 weighted image (Fig. 1b). The recuperation was complete after 2 weeks and the patient was disease-free at last check-up (March of 1995).

Discussion. Yang et al. (3) obtained a global response of 75% (50% with total recuperation and 25% with partial recuperation) in the patients treated with radiotherapy only. The global response was 66% in those treated with surgery followed by radiotherapy. Fox et al. (1) and Glanzman et al. (2) obtained a global response of 100% (4/4) and 70% (7/10) respectively in patients treated with surgery followed by radiotherapy. Other authors too had favorable results with this combined modality (5, 7–9, 11). The results obtained by Yang et al. (3) were the most precise in terms of describing the details of doses and scheduling used for radiotherapy (Table). Yang et al. (3) recommend a total dose of 30 to 40 Gy in a single course of 4 to 6 weeks' duration. They demonstrated that there is no difference between the administration of a single course or multiple courses. Additionally, they have accomplished a follow-up of 5 to 20 years during which time they did not find any relapse. In the series of Fox et al. (1) and Glanzman et al. (2), the treated patients were found to exhibit spinal cord compression without stating number of paraplegic cases. Fox et al. (1) does not detail a schedule of radiotherapy, nor do others reporting on combined modalities (4, 7–9). In addition, most of these authors do not report on the duration of follow-up in spite of the fact that VH can relapse long time after treatment (1, 6). In the revision by Krueger et al. (10), no significant differences were found in the number of patients who achieved full recovery through surgery followed by radiotherapy (61%) (43/70) or radiotherapy alone (59%) (26/44). In the series by Fox et al. (1), 2 out of 3 of the relapsed patients did not receive radiotherapy and the third received only 1 Gy postoperatively.



a) b)

Fig. 1. a) Sagittal T1w (500/20) MR scan: normal hyperintense signal is decreased, epidural intracanalicular lesion (on the left). b) Sagittal T1w (500/20) MR scan: the epidural lesion has disappeared (on the right).