The Management of Rhabdomyosarcoma in Children and Young Adults

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Survival rates among children with rhabdomyosarcoma have increased from approximately 20% to 70% during the past 15 years, and this improvement appears to be progressive. The major factor in this remarkable development has been the increasing effectiveness of multiple-agent, long-range chemotherapy regimens in (a) destroying micrometastasis, (b) controlling residual tumor at the sites of local excision, and (c) eliminating established metastatic tumor foci. Improved radiation therapy techniques and operative surgical procedures have been coordinated with this chemotherapeutic approach, largely in an adaptive fashion, resulting in multimodality therapy programs of increasing effectiveness. During the past decade, additional histologic variants of tumor have been identified, new techniques for accurately defining the extent of disease have been developed, and forms of vigorous supportive therapy have been employed for the first time. All of these have contributed to improvement in the results of therapy.

Incidence

In the United States, rhabdomyosarcoma represents between 5 and 15% of all malignant solid tumors, and 4-8% of all malignant diseases, found in children under 15 years of age [1-3]. In patients 21 years of age or younger, the incidence of rhabdomyosarcoma in the U.S.A. is probably greater than that of either neuroblastoma or nephroblastoma. Important recent information in regard to the incidence of rhabdomyosarcoma comes from the Intergroup Rhabdomyosarcoma Study (IRS), which registered more than 750 patients under 21 years of age in the 6-year interval from 1972-78 [4-6]. This study represents the largest and most completely analyzed group of pediatric and young adult patients with rhabdomyosarcomas, and will form the basis of much of this report. It should be noted, however, that approximately 15% of the tumors in patients in the IRS might not be regarded as rhabdomyosarcomas by conventional criteria. These have been classified in the past as "round cell sarcomas" or "undifferentiated soft tissue sarcomas." In those cases in which no other specific diagnosis could be established, they have been included in the IRS, although analyzed separately [6].

Tumor site is a factor in the incidence of rhabdomyosarcoma in different age groups. Tumors of the pelvic organs and head and neck are more prevalent in infancy and early childhood, while the para-
testicular rhabdomyosarcomas are largely a disease of adolescents or young adults. These factors result in two peaks in the overall incidence of rhabdomyosarcoma, one from birth to 4 years of age, and the second between 12 and 15 years of age [2]. The occurrence rates of rhabdomyosarcoma of the extremities are the same at all ages from early infancy through age 21 years, and in the smaller groups of primary orbital and trunk tumors, the incidence is also apparently unrelated to age.

Etiology and Epidemiology

The virus-induced neoplasm, described by Rouss in 1911, was probably a rhabdomyosarcoma, and several established oncogenic viruses produce rhabdomyosarcoma in animals [7, 8]. These tumor systems represent a field of continuing activity in the attempts to isolate a "human" tumor virus [9].

Families in which there is an increased incidence of carcinoma of the breast and other tumors frequently contain children with rhabdomyosarcomas [10], and the siblings of children with rhabdomyosarcoma have an increased incidence of soft tissue sarcomas, central nervous system neoplasms, and adrenocortical carcinomas. In the IRS there was an increased incidence of malformations, particularly of the central nervous system, in children with rhabdomyosarcoma [6]. However, rhabdomyosarcomas have not been associated with the current syndromes of endocrine-related neoplasms (multiple endocrine adenoma syndromes).

Pathology

Although classically described as occurring in striated muscle, rhabdomyosarcomas arise from a primitive cell type and can occur in mesenchymal tissue at almost any body site (possibly excluding the brain), including many organs that normally do not have striated muscle. The history of the separation of this tumor group from the large body of "soft tissue sarcomas" of children and young adults was gradual. Initially, only pleomorphic forms were recognized as rhabdomyosarcomas. The embryonal form was first described in detail by Stobbe and Dargeon in 1950 [11]. The rather diverse histologic types of rhabdomyosarcoma were united as a single entity (in which rhabdomyoblasts could be identified) during the period 1952–1958 [12], and the principal subtypes, pleomorphic, embryonal (including botryoid), and alveolar, were recognized as variants of a single tumor system. As improved techniques were developed to identify the rhabdomyoblast by light microscopy and the characteristic "bands" by electron microscopy, the segment of the soft tissue sarcoma group designated as rhabdomyosarcomas progressively increased. At the same time, new variants were identified within the category of rhabdomyosarcoma. In the IRS, 6 different histologic types are now described [6, 13].

Although tumors with all of the cell types occur in patients of any age, the predominant histologic type in infants and small children is embryonal. This form is found in more than 2/3 of the tumors of the head and neck, and approximately 1/2 of those in all other sites except the trunk, where it is less common than the alveolar form. The botryoid rhabdomyosarcoma is a subtype of the embryonal variety, which ordinarily extends into body cavities, such as the bladder, nasopharynx, vagina, or bile duct. These are usually grossly polypoid tumors, and the layers of small round cells at the periphery with a myxoid stroma give them a deceptively benign histologic appearance; however, rhabdomyoblasts can ordinarily be identified in this tissue. The alveolar cell type, named for a superficial resemblance to the pulmonary alveoli, is the most common form found in the muscle masses of the trunk and extremities, and is seen more frequently as age advances. Embryonal tumors, however, may also be found in adolescence and early adulthood. The pleomorphic type presents the most bizarre histologic appearance, with large elongated cells containing multiple nuclei, nuclei in tandem, or giant nuclei. When seen in children (1% of the IRS cases), these tumors are in the extremities or trunk. Most of the rhabdomyosarcomas have a preponderance of one cell type, although some have mixed components, usually embryonal and alveolar. When the diagnosis is uncertain, electron microscopy may reveal characteristic features, including primitive "Z bands" not visible by light microscopy, and immunofluorescence studies may be employed to establish the presence of myosin in the tumor cells, which identifies a myomatous tumor.

Among the 314 tumor specimens analyzed by the IRS pathology committee, two additional types, termed "soft tissue Ewing’s sarcoma" have been identified and divided on the basis of predominant cell size [13]. What appears to be the same tumor was described by the U.S. Armed Forces Institute of Pathology in 1975 [14]. The 26 IRS patients with these histologic features are of interest since these patients have shown the same rate of response to therapy as have patients with the generally recognized histologic types [6]. An additional small group of patients (6% of the IRS cases) is termed "small cell mesenchymal sarcomas, type undetermined," and contains patients in whom no more specific diagnosis is possible. These tumors have also responded to the therapy regimens designed for the