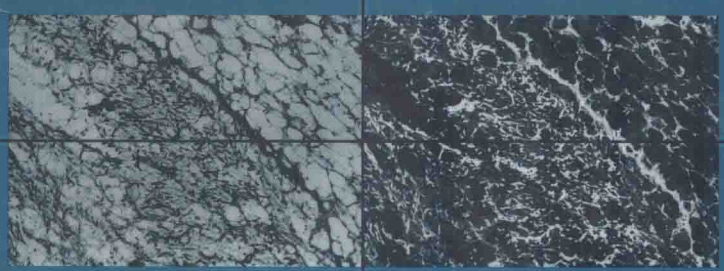
Pediatric Soft Tissue Tumors



A Clinical, Pathological, and Therapeutic Approach

Cheryl M. Coffin
Louis P. Dehner
Patricia A. O'Shea

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Cheryl M. Coffin, M.D.
Associate Professor of Pathology
Head, Division of Pediatric Pathology
University of Utah Health Science Center
Medical Director of Pathology Services
Primary Children's Medical Center
Salt Lake City, Utah

Louis P. Dehner, M.D.
Professor of Pathology
Director, Division of Anatomic Pathology
Washington University School of Medicine
Surgical Pathologist-in-Chief
Barnes Hospital
St. Louis, Missouri

Patricia A. O'Shea, M.D.
Associate Professor of Pathology
Emory University School of Medicine
Pediatric Pathologist
Egleston Children's Hospital at Emory University
Atlanta, Georgia

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Pediatric Soft Tissue Tumors

A Clinical, Pathological, and Therapeutic Approach

To those children whose past, present, and future tumors are the subject of this book, and to the men and women in the health professions who have provided and will provide their care

Foreword

It is both an honor and a pleasure to be asked to write the foreword to Drs. Coffin, Dehner, and O'Shea's book, *Pediatric Soft Tissue Tumors*. All three of the authors are long-time friends: two either are or have been professional colleagues, and one, Dr. Dehner, was a medical student here at Washington University, and I have watched his professional development since those early days. Because all three authors speak from extensive experiences in their present professional and academic affiliations and large consulting practices, what they have to say represents the cutting edge of facts and opinions on the topic of soft tissue tumors in children.

Immediately, the question must be addressed, "Why another book on soft tissue tumors and, more specifically, why a book addressed to soft tissue tumors in young patients?"

There are three answers to these questions, one ideologic and two practical. First, infants and children are not merely small adults. The subject of tumefactions of soft tissue in young patients includes many processes that are not neoplastic. Many, but not all of these processes, are developmental, such as some of the more common vascular proliferations of infancy and early childhood. The fibrous tumors of childhood, a group of unique entities, have received a thorough consideration.

Second, it must be acknowledged that many currently active pathologists received their training in programs with limited exposure to pediatric pathology material. This has led to a paradox: at the same time that modern molecular techniques such as immunohistochemistry, cytogenetics, and flow cytometry have become available in settings of patient care that once were characterized as "community hospitals," pathologists responsible for applying those techniques have progressively less experience in dealing with the presenting clinical and pathologic problems they encounter in young patients in their day-to-day clinical practices. Findings that are produced by these special studies, until recently the premises of research laboratories, are included in thorough discussions of each of the entities considered in this book, and recent references to the literature are cited. The three authors feel strongly that modern pathology not only participates but is essential in quality patient care.

Finally, tumefactions of soft tissue, while not common in the differential diagnosis, either clinical or pathological, in adult patients, are a substantial problem in pediatric oncology and pediatric pathology. In fact, speaking only of true neoplasms, somatic soft tissues rank either third or fourth most common as primary sites of origin of extracranial soft tissue tumors in infants and children.

A result of this relative infrequency has been that major interpretations regarding the natural history of many types of soft tissue tumors have of necessity been drawn from large intergroup cooperative studies from many centers. These studies, such as those originating from the Intergroup Rhabdomyosarcoma Study and the Kiel Pediatric Tumor Registry, have drawn major conclusions regarding the prognostic implications of pathologic find-

ings, especially histologic grade. These conclusions and the definitions of the pathologic parameters on which they have been based are thoroughly discussed and extensively tabulated in this volume.

In effect, this book makes highly qualified consultants as accessible to every pathologist as his or her bookshelf.

John M. Kissane, M.D.
Professor of Pathology and Pathology in Pediatrics
Washington University School of Medicine
St. Louis, Missouri

Preface

This book began with a question familiar to all surgical pathologists, "Is it benign or malignant, and how should the patient be treated?" The patient was a 1-month-old child with a large congenital tumor in the superficial soft tissue of the scalp. Experienced pathologists disagreed about the appropriate classification and diagnostic appellation for the lesion, and residents and fellows looked, listened, and pondered. Two of us visited the patient and reviewed the chart. While walking back from the hospital room, we discussed the legacies of eminent pathologists in the understanding of pediatric soft tissue lesions and the need for a more focused analysis of soft tissue tumors in children. The clinical question stimulated a series of projects spanning more than a decade. *Pediatric Soft Tissue Tumors* is the result, in part, of those studies and questions that emanated from the clinical problem presented in 1983. Our goal has been to understand the spectrum of pediatric soft tissue tumors more completely, using contemporary diagnostic techniques and concepts to assist pathologists and their clinical colleagues who are engaged in the diagnosis and care of affected children.

Any contribution to the contemporary literature in soft tissue pathology must acknowledge the work of several generations of eminent surgical pathologists, whose publications on soft tissue tumors are cited in the reference sections of all the chapters in this book.

As practicing diagnostic pathologists, we the editors experience on a daily basis the challenge of correctly diagnosing unusual soft tissue lesions in children. We also appreciate the generosity of many pediatric and general pathologists who have shared their interesting cases with us over the years and have provided their material, which has served as the important substrate for our studies. In addition, we appreciate the efforts and commitment of clinical contributors to this volume, who have provided a dimension to the diagnosis and treatment of soft tissue tumors well beyond our own experience.

We are grateful to many colleagues and friends throughout the general and pediatric pathology community and at our respective institutions for their guidance and encouragement during the preparation of this text. At Washington University in St. Louis, these include John Kissane, M.D., Michael Kyriakos, M.D., Emil Unanue, M.D., Jesse Ternberg, M.D., Teresa Vietti, M.D., Karen Perks, and Fran Buhr. Carlos Manivel, M.D., at the University of Minnesota provided valuable follow-up information. At Egleston Children's Hospital at Emory University, these include Carlos Abramowsky, M.D., Kevin J. Winn, M.D., Robert Pascal, M.D., Jackie Bradshaw, Vicki Lerch, and Vivian Otterbeck. At Primary Children's Medical Center and the University of Utah, Carl Kjeldsberg, M.D., Theodore Pysher, M.D., Joseph Horton, Joseph Mott, Linda Shields, Lorna Brown, Cherie Best, and Teresa Rawlings provided an environment in which it was possible to complete the project.

Last, but not least, our families have given unconditional love and support during the prolonged gestation of this manuscript. And the child with the tumor in question was alive and without evidence of recurrence more than ten years later.

Cheryl M. Coffin, M.D.
Louis P. Dehner, M.D.
Patricia A. O'Shea, M.D.

Contributors

Cheryl M. Coffin, M.D.

Associate Professor of Pathology
Head, Division of Pediatric Pathology
University of Utah Health Sciences Center
Medical Director of Pathology Services
Primary Children's Medical Center
Salt Lake City, Utah

Louis P. Dehner, M.D.

Professor of Pathology
Director, Division of Anatomic Pathology
Washington University School of Medicine
Surgical Pathologist-in-Chief
Barnes Hospital
St. Louis, Missouri

Patricia A. O'Shea, M.D.

Associate Professor of Pathology
Emory University School of Medicine
Pediatric Pathologist
Egleston Children's Hospital at Emory University
Atlanta, Georgia

L. Ellen Patrick, M.D.

Assistant Professor
Emory University School of Medicine
Department of Radiology (Pediatric)
Egleston Children's Hospital at Emory University
Atlanta, Georgia

John R. Priest, M.D.

Department of Pediatric Hematology/Oncology
Children's Health Care–St. Paul
St. Paul, Minnesota

Deborah E. Schofield, M.D., M.B.A.

Assistant Professor
Department of Pathology
Harvard Medical School and Children's Hospital
Boston, Massachusetts

Steven M. Scott, M.D.

Clinical Assistant Professor
Department of Orthopaedics
University of Utah
Salt Lake City, Utah

Lynn M. Smith, M.D.

Assistant Professor
Department of Radiation Oncology
University of Utah
Salt Lake City, Utah

Jan Watterson, B.A.

Research Assistant
Department of Hematology/Oncology
Children's Health Care–St. Paul
St. Paul, Minnesota

Contents

1

Some General Considerations about the Clinicopathologic Aspects of Soft Tissue Tumors

Louis P. Dehner

Most physicians, regardless of their practice, have some general ideas and concepts about soft tissue tumors. There is generally an appreciation that the types of soft tissue tumors that occur in children are different, for the most part, from those that are seen in adults, if for no other reason than that many categories of pathologic processes in children are distinct from those in adults. The pathologic themes of childhood are natural and unnatural accidents, consequences of an adverse intrauterine environment, complications of premature birth, infections with devastating effects upon the young host, and a compendium of unique neoplasms whose morphologic features are an attempt to recapitulate the developmental phases of a particular tissue or organ. This idea of the "borderland between embryology and pathology" was emphasized by Willis in his classic treatise on pediatric pathology (1). By contrast, the pathologies of adulthood are manifestations of the cumulative effects of life, which eventually may unmask a hereditary defect whose phenotypic expression has been facilitated by habits of lifestyle that promote the development of atherosclerosis, destruction of an organ like the liver, and cancers of various types.

This chapter introduces the broad subject of soft tissue tumors in children. Those who can recall 25–30 years ago can appreciate the substantial progress that has been made in the diagnosis and treatment of soft tissue neoplasms in the pediatric population. Very few malignant small cell tumors remain any longer in the category of an undifferentiated small blue cell neoplasm. Where once radical and sometimes disfiguring surgery was the only available therapeutic modality, today combinations of treatment have evolved to the degree that long-term survival has ceased to be a curiosity and is now a reasonable expectation by the parents and those who are treating the patient. Although gaps still exist in our knowledge and understanding about the pathogenesis and histogenesis of soft tissue neoplasms in children, and adults for that matter, there is a level of insight about soft tissue tumors in

children today that could not have been anticipated a quarter of a century ago. The subsequent chapters in this volume serve as tangible testimonies to the current level of our understanding about many soft tissue tumors, but simultaneously will make clear those areas that still require our attention. The topic of soft tissue tumors in children is like children in general—works in progress.

Upon initial reflection, the definition of a soft tissue tumor may appear to be self-evident; but is it? In adults, a soft tissue tumor generally implies a soft tissue neoplasm arising in the subcutaneous and deep tissues of the extremities, trunk, retroperitoneum, and head and neck region, in this approximate order of frequency. Many of these neoplasms are clonal, regardless of the benign or malignant nature, and have a repetitive cytogenetic abnormality (2, 3). In children, most soft tissue tumors are neoplasms, but some are thought to be tumorlike malformations or hamartomas, such as the cystic hygroma or lymphangioma. There are examples of soft tissue tumors in children that are difficult to categorize pathogenetically as a hamartoma or a neoplasm. Fetal rhabdomyoma is an example of a soft tissue tumor whose pathogenesis as a hamartoma or neoplasm remains an unsettled issue. The dysmorphologies of neurofibromatosis, Proteus syndrome, and Klippel-Trenaunay-Weber syndrome are three examples of conditions in which some of the soft tissue masses are clearly neoplasms and others are hamartomas. The plexiform neurofibroma of neurofibromatosis type 1 is included in most classifications of soft tissue neoplasms, but it could be argued that this tumor is a malformation in the growth of a peripheral nerve. Most soft tissue neoplasms in adults arise in the peripheral soft tissues of the extremities, but in children, vascular and rhabdomyogenic neoplasms, the most common categories of benign and malignant soft tissue tumors, have a preference for the soft tissues of the head and neck region and the genitourinary tract (5).

An assumption has been made to this point that there is a common understanding of the composition of the soft tissues and the types of neoplasms that morphologically reflect one of the constituent mesenchymal tissues. The elements of the soft tissues include fat, blood vessels and lymphatics, fibrous tissue, nerves, and smooth and skeletal muscle. There are neoplastic counterparts for each of these structural components of the soft tissues, but there are also soft tissue neoplasms whose normal cellular counterparts are not so easily defined in the conventional scheme of normal soft tissues. For instance, myofibroblasts in the resting soft tissues are not readily identifiable, although they are a principal cell type in a reparative process or the desmoplastic stroma of an infiltrating carcinoma of the breast (4). The all-purpose myofibroblast is the cell type of myofibromatosis and desmoid tumor, but is it also the progenitor of the fibrous histiocytoma? Where is the normal counterpart of the malignant cells of alveolar soft part sarcoma or the granular cells of the granular cell tumor? The phenotype of a soft tissue neoplasm is only that in many cases, since the cell of origin is very likely not a resting differentiated cell, but an uncommitted stromal or mesenchymal cell. This seems particularly true when the soft tissue neoplasm is a sarcoma. It is also possible that the histogenesis of a benign soft tissue neoplasm is different in some unspecified manner than a sarcoma; however, clonality is not dependent on the benign or malignant nature of a soft tissue tumor (2, 3). There is still the lingering tendency to regard the phenotype as a reflection of ontogeny, which is unlikely in many instances.

Just as Wilms' tumor attempts to resemble developing kidney, so several of the unique soft tissue neoplasms in children have histologic features of developing tissue or mesenchymal structures in the fetus. There is a similarity between embryonic and fetal muscle and embryonal rhabdomyosarcoma and fetal rhabdomyoma (5). In fact, some of the molecular mechanisms involved in normal myogenesis have been identified in childhood rhabdomyosarcomas (6). The appearance of a lipoblastoma in a child resembles fetal fat, whereas a well-differentiated or lipomalike liposarcoma in an adult has the appearance of mature adipose tissue (7).

Soft Tissue Tumors in Children

It is difficult to acquire comparative data on the relative incidence and clinical importance of soft tissue tumors in the pediatric versus adult populations. In our experience, a small superficial tumor in a child is more likely to be biopsied or excised than is a comparably sized lesion in an adult for the obvious reasons of parental concern. Is a soft tissue neoplasm in a child more or less likely to be benign or malignant than in an adult? The answer is not clear from the available literature. From the perspective of a general surgical pathology practice, many lipomas from adults pass beneath the objective of the microscope before one of the more common soft tissue sarcomas in adults, the liposarcoma, is encountered. One only has to relate this experience with fatty tumors in adults to appreciate the infrequency of a fibromatosis or an embryonal rhabdomyosarcoma in a child. On the other hand, hemangiomas and cystic hygromas in young children are seen more frequently, since vascular tumors of one type or another are the single largest category of soft tissue tumors in children (8). Approximately 30% of soft tissue tumors in children were vascular in nature in a review of over 900 benign and malignant soft tissue neoplasms diagnosed in the first two decades of life during a 25-year period, whereas fibrohistiocytic and lipocytic tumors accounted for 17 and 15% of cases, respectively, in the predominantly adult population of patients with soft tissue neoplasms on file during a 10-year period at the Armed Forces Institute of Pathology (9–11) (Table 1.1). Myogenic neo-

Table 1.1. Categories of Soft Tissue Tumors in Children and Adults

Tumor Categories	*Children (%)*	*Adults (%)*
Vascular	29	9
Neurogenic	15	9
Myogenic	14	5
Fibroblastic-myofibroblastic	12	7
Fibrohistiocytic	12	17
Lipocytic	6	16
Other	12	38
	100	100

Data adapted from Refs. 9–11.

plasms as a percentage of the total are considerably more common in children than in adults; rhabdomyosarcoma accounted for 98% of myogenic neoplasms in children, whereas leiomyoma and leiomyosarcoma, representing 2 and 8%, respectively, of all soft tissues tumors in adults, comprised 85% of myogenic tumors in the adults (10, 11). Fibroblastic and myofibroblastic tumors comprise a higher proportion of soft tissue tumors in children than in adults, but a more important difference between the two age groups is the subtypes of fibrous tumors found in children and adults. Infantile myofibromatosis, musculoaponeurotic fibromatosis and fibromatosis colli account for 50% of all tumors of fibroblastic-myofibroblastic derivation in children (9). In adults, palmar and plantar fibromatosis (superficial fibromatosis) and extraabdominal desmoid tumor are the two most common myofibroblastic tumors (9). Several other fibroblastic-myofibroblastic tumors are found almost exclusively in children, including digital fibromatosis, fibrous hamartoma of infancy, and congenital-infantile fibrosarcoma (9, 12). A majority of fibrohistiocytic neoplasms in adults are malignant fibrous histiocytomas, which is a rarely occurring tumor in children (8, 9, 13–17). Most fibrous histiocytomas in children present in the skin and subcutis, and many of these, especially in younger children, are often fibrohistiocytic variants of juvenile xanthogranuloma (18). Lipomatous neoplasms in children are substantially less common than they are in adults (8–11). Most fatty tumors in children are lipoblastomas or suspected lipoblastomas with adult lipomalike features (7).

Classification

Some categories of neoplasms seem to attract a disproportionate amount of time, attention, and effort into the construction and organization of classifications. These various tumor types include the malignant lymphomas and leukemias and neoplasms of the skeletal system and soft tissues. Each of these categories of neoplasms is characterized by a number of distinct entities, reflecting in part the complex nature of the organ system or the diversity of tissue types in the case of soft tissues.

The principle that has guided the classification of soft tissue neoplasms is the morphologic resemblance of the tumor in question to one of the component mesenchymal tissues. The pathologic diagnosis of embryonal rhabdomyosarcoma in the past was predicated upon the identification of cytoplasmic cross-striations as normal skeletal muscle; this exercise may have required a tedious cell-by-cell examination, which was facilitated in some cases with a phosphotungstic acid-hematoxylin stain. With the application of electron microscopy, it became possible to identify thick and thin filaments in embryonal rhabdomyosarcomas which were more primitive and did not have organized sarcomeres (18). However, the small sample size, for reasons of fixation and sectioning, reduced the number of tumor cells that could be examined compared with the number that could be examined using routine histology. The advent of immunohistochemistry shifted the traditional paradigm of morphologic structure to the molecular properties of the cell as a function of structure. Structural phenotype has yielded to immunophenotype in the contemporary diagnosis of soft tissue neoplasms and many other types of tumors. For example, positive staining with antibodies directed against muscle-specific actin and desmin is considered sufficient for the diagnosis of embryonal rhabdomyosarcoma without the requirement for the identification of cross-striations by light microscopy or thick and thin filaments by electron microscopy. More recently, tumor cytogenetics has evolved to the point that one can foresee the day when a repetitive translocation or deletion may become the "gold standard" for the diagnosis of some tumors, including soft tissue neoplasms, rather than the morphologic features. A window into the future has been the discovery of the t(11;22)(q24;q12) translocation in Ewing's sarcoma and primitive neuroectodermal tumor, which has served as the prototype in pathology of soft tissues. Future classifications of soft tissue neoplasms undoubtedly will have a heading entitled, "Ewing family of tumors," based upon the involvement of the EWS gene in various translocations (20, 21) (see Chapter 12).

Until the time arrives when molecular biology eclipses the morphologic-based classifications of tumors, we will continue to use the standard approach as the World Health Organization's (WHO) *Histologic Typing of Soft Tissue Tumors,* as proposed by Weiss and several other well-known soft tissue pathologists (22). This classification recognizes 12 phenotypic categories of tumor and tumorlike lesions ranging from fibrous to chondroid and osseous tumors of soft tissues, mesenchymoma as a pluripotential mesenchymal neoplasm, and tumors of miscellaneous types (Table 1.2). All of the principal types of soft tissue neoplasms with a predilection to children are included in the WHO classification. However, no attempt has been made to set aside or specifically designate those neoplasms of soft tissues of particular interest and predisposition to the pediatric age group. There are some peculiarities in the classifi-

Table 1.2. World Health Organization's Histological Classification of Soft Tissue Tumors[a]

1. Fibrous tissue tumor
   - Benign
     - Fibroma
     - Keloid[2]
     - Nodular fasciitis[2]
     - Proliferative fasciitis[3]
     - Proliferative myositis[3]
     - Elastofibroma[3]
     - Fibrous hamartoma of infancy[1]
     - Myofibromatosis, solitary and multicentric[1]
     - Fibromatosis colli[1]
     - Calcifying aponeurotic fibroma[1]
     - Hyaline fibromatosis[1]
   - Fibromatosis
     - Superficial fibromatosis
       - Palmar and plantar fibromatosis[2]
       - Infantile digital fibromatosis (digital fibroma)[1]
     - Deep fibromatosis
       - Abdominal fibromatosis (desmoid tumor)[2]
       - Extraabdominal fibromatosis (desmoid tumor)[2]
       - Intraabdominal and mesenteric fibromatosis[2]
       - Infantile fibromatosis[1]
   - Malignant
     - Fibrosarcoma
     - Adult fibrosarcoma[3]
     - Congenital or infantile fibrosarcoma[1]
2. Fibrohistiocytic tumors
   - Benign
     - Fibrous histiocytoma
     - Cutaneous histiocytoma (dermatofibroma)[2]
     - Deep histiocytoma[2]
     - Juvenile xanthogranuloma[1]
     - Reticulohistiocytoma[3]
     - Xanthoma[3]
   - Intermediate
     - Atypical fibroxanthoma[3]
     - Dermatofibrosarcoma protuberans[2]
     - Pigmented dermatofibrosarcoma protuberans (Bednar tumor)[2]
     - Giant cell fibroblastoma[1]
     - Plexiform fibrohistiocytic tumor[2]
     - Angiomatoid fibrous histiocytoma[2]
   - Malignant
     - Malignant fibrous histiocytoma
       - Storiform-pleomorphic[3]
       - Myxoid[3]
       - Giant cell[3]
       - Xanthomatous (inflammatory)[3]
3. Lipomatous tumors
   - Benign
     - Lipoma[2]
     - Lipoblastoma (fetal lipoma)[1]
     - Lipomatosis[2]
     - Angiolipoma[2]
     - Spindle cell lipoma[3]
     - Pleomorphic lipoma[3]
     - Angiomyolipoma[2]
     - Myelolipoma[3]
     - Hibernoma[3]
     - Atypical lipoma[3]
   - Malignant
     - Well-differentiated liposarcoma[3]
       - Lipomalike
       - Sclerosing
     - Inflammatory[3]
     - Myxoid liposarcoma[2]
     - Round cell (poorly differentiated myxoid) liposarcoma[3]
     - Pleomorphic liposarcoma[3]
     - Dedifferentiated liposarcoma[3]
4. Smooth muscle tumors
   - Benign
     - Leiomyoma[2]
     - Angiomyoma[2]
     - Epithelioid leiomyoma[2]
     - Leiomyomatosis peritoneales disseminata[3]
   - Malignant
     - Leiomyosarcoma[3]
     - Epithelioid leiomyosarcoma[3]
5. Skeletal muscle tumor
   - Benign
     - Rhabdomyoma
       - Adult[3]
       - Genital[2]
       - Fetal[1]
   - Malignant
     - Rhabdomyosarcoma
       - Embryonal rhabdomyosarcoma[1]
       - Botryoid rhabdomyosarcoma[1]
       - Spindle cell rhabdomyosarcoma[1]
       - Alveolar rhabdomyosarcoma[1]
       - Pleomorphic rhabdomyosarcoma[3]
     - Rhabdomyosarcoma with ganglionic differentiation[1] (ectomesenchymoma)
6. Endothelial tumors of blood and lymph vessels
   - Benign
     - Papillary endothelial hyperplasia[2]
     - Hemangioma
       - Capillary hemangioma[2]
       - Cavernous hemangioma[2]
       - Venous hemangioma[2]
       - Epithelioid hemangioma (angiolymphoid hyperplasia, histiocytoid hemangioma)[2]
       - Pyogenic granuloma (granulation tissue type hemangioma)[2]
       - Acquired tufted hemangioma (angioblastoma)[2]
     - Lymphangioma[2]
     - Lymphangiomyoma[2]
     - Lymphangiomyomatosis[2]
     - Angiomatosis[2]
     - Lymphangiomatosis[1]
   - Intermediate: Hemangioendothelioma
     - Spindle cell hemangioendothelioma[2]
     - Endovascular papillary angioendothelioma (Dabska tumor)[1]
     - Epithelioid hemangioendothelioma[2]
   - Malignant
     - Angiosarcoma[3]
     - Lymphangiosarcoma[3]
     - Kaposi's sarcoma[3]
7. Perivascular tumors
   - Benign
     - Benign hemangiopericytoma[2]

Table 1.2.—*continued*

- Glomus tumor[2]
- Malignant
  - Malignant hemangiopericytoma[3]
  - Malignant glomus tumor[3]
8. Synovial tumors
   - Benign
     - Tenosynovial giant cell tumor
       - Localized[2]
       - Diffuse (extraarticular pigmented villonodular synovitis)[2]
   - Malignant
     - Malignant tenosynovial giant cell tumor[3]
9. Mesothelial tumors
   - Benign
     - Solitary fibrous tumor of pleura and peritoneum[3] (localized fibrous mesothelioma)
     - Multicystic mesothelioma[2]
     - Adenomatoid tumor[3]
     - Well-differentiated papillary mesothelioma[2]
   - Malignant
     - Malignant solitary fibrous tumor of pleura and peritoneum (malignant localized fibrous mesothelioma)
     - Diffuse mesothelioma[2]
       - Epithelial
       - Spindled (sarcomatoid)
       - Biphasic
10. Neural tumors
    - Benign
      - Traumatic neuroma[2]
      - Morton neuroma[3]
      - Neuromuscular hamartoma[1]
      - Nerve sheath ganglion[2]
      - Schwannoma (neurilemoma)[2]
      - Plexiform schwannoma[2]
      - Cellular schwannoma[2]
      - Degenerated (ancient) schwannoma[3]
      - Neurofibroma
        - Diffuse[2]
        - Plexiform[2]
        - Pacinian[2]
        - Epithelioid[2]
      - Granular cell tumor[2]
      - Melanocytic schwannoma[3]
      - Neurothekeoma (nerve sheath myxoma)[2]
      - Ectopic meningioma[2]
      - Ectopic ependymoma[2]
      - Ganglioneuroma[2]
      - Pigmented neuroectodermal tumor of infancy (retinal enlage tumor, melanotic progonoma)[1]
    - Malignant
      - Malignant peripheral nerve sheath tumor (MPNST) (malignant schwannoma, neurofibrosarcoma)
        - MPNST with rhabdomyosarcoma (malignant triton tumor)[2]
        - MPNST with glandular differentiation[2]
        - Epithelioid MPNST[2]
      - Malignant granular cell tumor[2]
      - Clear cell sarcoma (malignant melanoma of soft parts)[2]
      - Malignant melanotic schwannoma[2]
      - Neuroblastoma[1]
      - Ganglioneuroblastoma[1]
      - Neuroepithelioma (peripheral neuroectodermal tumor, peripheral neuroblastoma)[2]
11. Paraganglionic tumors
    - Benign
      - Paraganglioma[2]
    - Malignant
      - Malignant paraganglioma[2]
12. Cartilage and bone tumors
    - Benign
      - Panniculitis ossificans[3]
      - Myositis ossificans[2]
      - Fibrodysplasia (myositis) ossificans progressiva[1]
      - Extraskeletal chondroma[2]
      - Extraskeletal osteochondroma[2]
      - Extraskeletal osteoma[2]
    - Malignant
      - Extraskeletal chondrosarcoma[2]
        - Well-differentiated chondrosarcoma
        - Myxoid chondrosarcoma
        - Mesenchymal chondrosarcoma
        - Dedifferentiated chondrosarcoma
      - Extraskeletal osteosarcoma[3]
13. Pluripotential mesenchymal tumors
    - Benign
      - Mesenchymoma[2]
    - Malignant
      - Malignant mesenchymoma[2]
14. Miscellaneous tumors
    - Benign
      - Congenital granular cell tumor[1]
      - Tumoral calcinosis[2]
      - Myxoma
        - Cutaneous[2]
        - Intramuscular[3]
      - Angiomyxoma[2]
      - Amyloid tumor[3]
      - Parachordoma[2]
      - Ossifying fibromyxoid tumor[2]
      - Juvenile angiofibroma[1]
      - Inflammatory myofibroblastic tumor (inflammatory fibrosarcoma)[2]
    - Malignant
      - Alveolar soft part sarcoma[2]
      - Epithelioid sarcoma[2]
      - Extraskeletal Ewing sarcoma[2]
      - "Synovial" sarcoma[2]
        - Monophasic fibrous type
      - Malignant (extrarenal) rhabdoid tumor[1]
      - Desmoplastic small cell tumor of children and young adults[2]
15. Unclassified tumors

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[a]Key: [1]Most tumors of this type present before the age of 20 years.

[2]Although this tumor is known to present more often in children than in adults, it is not strictly considered a neoplasm of either age group.

[3]More than 90% of cases present in patients beyond the third decade of life.

cation in regard to the fibrous tissue tumors, which are divided into three subcategories: benign, fibromatosis, and malignant. Fibrous hamartoma of infancy, myofibromatosis, fibromatosis colli, calcifying aponeurotic fibroma, and hyaline fibromatosis, all of which occur almost exclusively in children, are found in the same benign fibrous tumor category as the keloid, nodular fasciitis, and elastofibroma, and are separate from the fibromatoses. Infantile digital fibromatosis and infantile fibromatosis are classified with the fibromatoses. There is considerable merit to the separation of the unique fibrous tumors of childhood from the adult varieties while recognizing that there is clinical overlap with desmoid tumors in infants and infantile myofibromatosis in adults. Congenital-infantile fibrosarcoma is appropriately designated as a distinct entity from adult fibrosarcoma in the category of malignant fibrous tumors, although the histopathologic features of congenital-infantile and adult fibrosarcomas may be indistinguishable in some cases. As discussed elsewhere, the pattern of congenital-infantile fibrosarcoma may be found adjacent to foci of infantile myofibromatosis, hemangiopericytoma, and infantile fibromatosis in a single soft tissue mass from an infant; these mixed-pattern fibrous tumors in children illustrate the limitations inherent to any classification, since it is virtually impossible to anticipate every permutation and combination in some neoplasms.

Soft tissue tumors in the WHO classification can be divided into three general categories on the basis of their predilection in children or adults: (*a*) a tumor almost exclusive to children; (*b*) a tumor with a predilection to children or adults, but known to occur in both age groups, but one or the other age group may be favored in the particular category of tumor; and (*c*) a tumor almost exclusive to adults. One of the quintessential soft tissue neoplasms of childhood is the rhabdomyosarcoma (RMS), whose two major subtypes, alveolar and embryonal RMS, have been designated collectively as juvenile RMS by Bale and associates (23) to be distinguished from the rare pleomorphic rhabdomyosarcoma in the adult. The Intergroup Rhabdomyosarcoma Study has proposed a clinicopathologic classification of childhood RMS that recognizes three prognostic groups based upon the subtype of RMS: superior prognosis (botryoid and spindle RMS), intermediate (embryonal RMS), and poor (alveolar RMS and undifferentiated sarcomas) (24). A fourth category is the RMS with rhabdoid features whose prognostic implications were not certain, although Kodet and associates (25) concluded that rhabdoid morphology did not have an adverse effect upon the clinical outcome of an otherwise favorable type of RMS. As RMS and all other sarcomas are classified by the WHO, prognosis is not considered directly, except for the differences in behavior, on the basis of tumor subtype. Two categories of soft tissue neoplasms, the fibrohistiocytic tumors and endothelial tumors of blood vessels and lymphatics, each have an intermediate or indeterminant prognostic group, since the clinical outcome is not predictable; on the basis of tumor type, most prognostically intermediate neoplasms have benign behavior, whereas others are locally aggressive and a few are known to metastasize. Several of the intermediate fibrohistiocytic and vascular neoplasms have a preferential occurrence in children, including the giant cell fibroblastoma, plexiform fibrohistiocytic tumor, angiomatoid fibrous histiocytoma, and endovascular papillary angioendothelioma (see Chapters 3 and 6).

The sobriquet, malignant small blue cell tumors of childhood, is familiar to most pediatric and surgical pathologists from the perspective of differential diagnostic implications. Two neoplasms in the differential diagnosis of small blue cell neoplasms, extraskeletal Ewing's sarcoma and desmoplastic small round cell tumor, are found in the category of "malignant miscellaneous tumors" in the WHO classification (Table 1.2). Despite the widely acknowledged fact that extraskeletal Ewing's sarcoma and primitive neuroectodermal tumor are closely related entities, arguably more so than many other neoplasms within a single nosologic group, they remain separated across the boundaries of current classification (21, 22, 26, 27). Classifications in the future may find primitive neuroectodermal tumor, Ewing's sarcoma, desmoplastic small round cell tumor, malignant melanoma of soft tissues, and possibly other tumors such as extraskeletal myxoid chondrosarcoma and malignant rhabdoid tumor in the category of the Ewing's sarcoma family.

One tumor in the "benign miscellaneous" group of importance in childhood is the inflammatory myofibroblastic tumor (IMT), or inflammatory pseudotumor (28). The literature has presented the argument that the IMT is not only a neoplasm, but is a malignant one, with the designation of inflammatory fibrosarcoma (29). Like nodular fasciitis and infantile myofibromatosis, the myofibroblast is the most prominent proliferative component of the IMT, yet this tumor is not included with the other fibrous tumors. Infiltrative growth, multifocal lesions in some cases, and local recurrences are features in common with the fibromatoses, but, in contrast to the benign fibrous tumors and fibromatoses, malignant progression is seen in 1–2% of IMTs (28). A few tumors have been shown to be clonal, and Epstein-Barr virus has been detected in a few examples of hepatic, splenic, and lymph nodal IMT. When classifications of soft tissue neoplasms are revised at a later date, IMT may reasonably find a niche in the newly created category of "intermediate" fibrous tumors.

Soft Tissue Sarcomas

Over a year, 6000 soft tissue sarcomas are newly diagnosed in the adult population in the United States as compared with approximately 600 cases of soft tissue sarcomas in children younger than 15 years of age (30–36). Soft tissue sarcomas represent 1% or less of all