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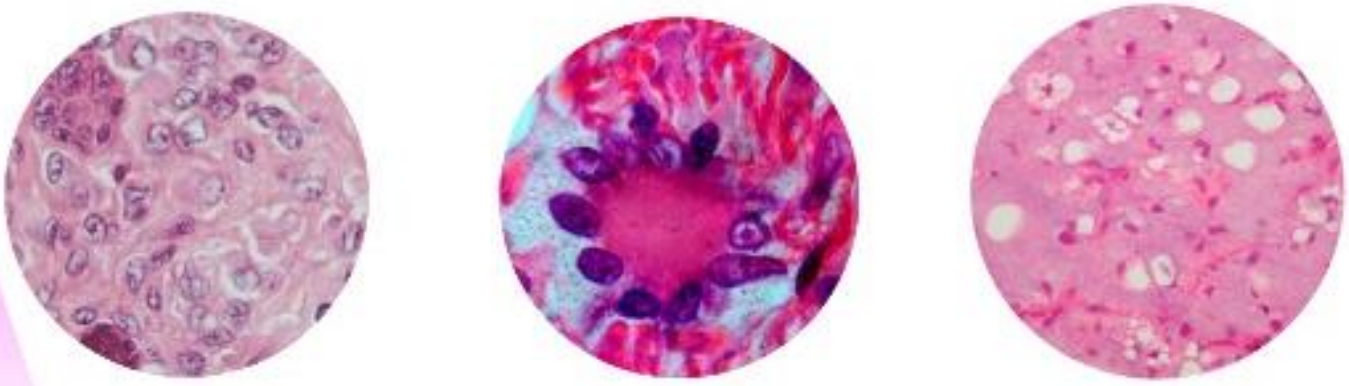

9-10 October 2020

PROCEEDINGS BOOK

Proceedings Book

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Organization - Committees

Organization

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Under the Auspices of

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Welcome Message

Ioannina University Courses in Pathology (IUCP) are organized in Ioannina, Greece every year. These are postgraduate courses on selected topics of Human Pathology and have been offered since 1996, after the unanimous decision of the Executive Committee (Brussels, June 1995) of the European Society of Pathology, to give the ESP auspices to the organization of the IUCP.

Since the beginning, the aim of the courses is to bring together young Pathologists and Tutors, experts in the various fields of Pathology, as well as to encourage active participation of all colleagues during the discussions following the Lectures and the Slide Seminars, providing an in-depth review of Diagnostic Surgical Pathology. An emphasis is given on morphologic features, newly recognized entities and modern techniques. The Courses have been designed for 45-50 Pathologists and Clinical Colleagues related to the subject.

Starting from 2017, the organization of IUCP has been passed by Em. Prof. NJ Agnantis to the Hellenic Society of Pathology (HSP), and she has been nominated Honorary President of IUCP. For 2020, HSP is offering the 37th IUCP on **Soft Tissue Pathology-Oncology**. The 2020 IUCP was originally planned to be held in Ioannina, from 13-15 of March, but due to the COVID pandemic we were not able to host our distinguished faculty and attendees. Our commitment to training of young Pathologists and to continuing education of senior Pathologists, prompted us to convert the Ioannina-based course to a WEB Scientific event, to be offered from 9 to 10 of October 2020.

We thank the Speakers and Chairpersons who, despite pressing schedules, adapted willingly to the new format of the Course and participated in memorable Sessions. We also thank our participants/students, and encourage them to web-interact during the presentations.

We do hope that the presentations by experts on the field will meet your expectations and will increase your knowledge in this particular field of Pathology. We all greatly miss the in-person interactions during the Sessions, but also during the social events. The latter, together with the high quality of the scientific content have made IUCP famous worldwide. We can only promise that we shall meet again in Ioannina for the next IUCPs to come.

Prof. Anna Batistatou
President of
Hellenic Society of Pathology

Dr. Kalliopi Patsiaoura
Secretary General of
Hellenic Society of Pathology

Dedicated to the memory of

The IUCP 2020 is dedicated to the memory of our dearest colleague **IOANNIS EFSTRATIOU**, who was Head of Department of Pathology in the General Hospital "Papageorgiou" in Thessaloniki, from November 2000.

He was an elected member of the Advisory Board of Hellenic Society of Pathology (HSP) for 2 years (2012-2014).

He was coordinator of the Soft tissue and Bone HSP Working Group and also participated as a member in the Lung HSP Working Group.

We remember his important lectures about the History of Medicine and Surgical Pathology, in several congresses held by the Hellenic Society of Pathology.

Ioannis Efstratiou was an exceptional scientist and we will always remember him.

Scientific Programme

Friday, 9th October 2020

14.45-15.00 Welcome Notes

15.00-15.30 **LECTURE**
Chairpersons: **Ass. Prof. A. Mitselou (GR), Assoc. Prof. D. Peschos (GR)**

Histology of Mesenchymal Tissue
Ass. Prof. V. Galani (GR)

15.30-16.30 **SESSION I**
Chairpersons: **Dr. S. Kamina (GR), Dr. A. Zizi (GR)**

15.30-16.00 Introduction of Soft Tissue Tumor Pathology: Classification and Grading
Dr. A. Nikolaidou (GR)

16.00-16.30 Immunohistochemical and Molecular Pathology in Diagnosis of Soft Tissue Tumours
Dr. S. Sotiriou (GR)

16.30-18.00 **SESSION II**
Chairpersons: **Ass. Prof. A. Papoudou-Bai (GR), Dr. E. Patsea (GR), Dr. A. Zioga (GR)**

16.30-17.15 The Most Common Spindle Cell Tumors of Deep Soft Tissue in Adults: Diagnostic Approach
Dr. E. Skarpidi (GR)

17.15-18.00 Gastrointestinal Stromal Tumors
Assoc. Prof. G. Agrogiannis (GR)

18.00-18.15 B r e a k

18.15-20.15 **SESSION III**
Chairpersons: **Dr. E. Giannikaki (GR), Dr. A. Nikolaidou (GR), Dr. K. Patsiaoura (GR)**

Undifferentiated small round cell sarcomas other than Ewing sarcoma
Ass. Prof. K. Linos (USA)

Pearls and pitfalls of selected immunohistochemical stains in cutaneous mesenchymal tumors
Ass. Prof. K. Linos (USA)

20.15-20.45 OPENING LECTURE
Chairpersons: Prof. A. Batistatou (GR), Prof. A. Goussia (GR)

IUCP History
Em. Prof. N. J. Agnantis (GR)

Saturday, 10th October 2020

09.00-10.30 SESSION IV
Chairpersons: Dr. S. Mavropoulou (GR), Dr. A. Sourla (GR)

09.00-10.00 Vascular Tumors
Prof. P. Korkolopoulou (GR)

10.00-10.30 Slide Seminar I
Cases 1-3: Dr. Z. Evangelou (GR), Prof. A. Batistatou (GR)
Cases 4-6: Dr. M. Kilmpasani (GR), Prof. A. Batistatou (GR)

10.30-12.15 SESSION V
Chairpersons: Prof. A. Batistatou (GR), Prof. V. Zolota (GR)

10.30-12.15 Pleomorphic Soft Tissue Tumors: A Diagnostic Algorithm and Slide Seminar II
Dr. Prof. D. Creytens (BEL)

12.15-13.45 SESSION VI
Chairpersons: Assoc. Prof. G. Agrogiannis (GR), Dr. M. Bobos (GR), Dr. D. Bouklas (GR)

12.15-12.45 An Approach of Epithelioid Soft Tissue Tumors
Dr. K. Diamantopoulou (GR)

12.45-13.15 Update on Myxoid Soft Tissue Tumors
Dr. D. Mourtzoukou (GR)

13.15-13.45 Pseudosarcomas of Soft Tissues
Prof. D. Papachristou (GR)

13.45-14.45 B r e a k

14.45-15.30 Slide Seminar III
Chairpersons: **Dr. P. Arapantoni-Dadioti (GR), Dr. M. Demonakou (GR), Dr. O. Tzaida (GR)**

Cases: **Prof. D. Papachristou (GR)**

15.30-16.30 Satellite Symposium
(please see page 10)

16.30-17.30 **SESSION VII**
Chairpersons: **Ass. Prof. T. Koletsa (GR), Em. Prof. S. Scopa (GR)**

16.30-17.00 Site Specific Soft Tissue Tumors
Dr. Siozopoulou V. (BEL)

17.00-17.30 The Role of the Oncologist
Dr. Zarkavelis G. (GR)

17.30-18.30 Slide Seminar IV
Chairpersons: **Dr. A. Nikolaidou (GR), Dr. S. Papaemmanouil (GR), Prof. V. Zolota (GR)**

Case 1: **Dr. S. Mavropoulou (GR)**
Case 2: **Dr. M. Kilmpasani (GR), Dr. S. Papaemmanouil (GR)**
Case 3: **Dr. G. Balis (GR)**
Case 4: **Dr. S. Sotiriou (GR)**
Case 5,6: **Dr. S. Sakellariou (GR)**

18.30-19.00 Closing remarks
Chairpersons: **Prof. A. Batistatou (GR), Dr. K. Patsiaoura (GR), Prof. V. Zolota (GR)**

Histology of Mesenchymal Tissue

Vasiliki Galani
Associate Professor of Anatomy-Histology-Embryology, Faculty of Medicine, University of Ioannina, Greece

Introduction

Soft tissue is a broad term often used for mesenchymal tissue that support and surround more well-defined organs and specific tissues. The cells and structures of soft tissue are present throughout the human body. The major cell types of soft tissues are non-epithelial and of mesodermal origin, denoted as "mesenchymal cells".
Mesenchyme is embryonic connective tissue, with appearance Gel-like ground substance with fibers and star-shaped mesenchymal cells. It gives rise to all other connective tissues. Mesenchymal cells can migrate easily, in contrast to epithelial cells, which lack mobility, are organized into closely adherent sheets, and are polarized in an apical-basal orientation.

The greatest amount of bulk of the body is composed of the cells forming tissues that are considered "soft" tissues or connective tissues. These are embryologically derived from the mesoderm. Hence, they are often called "mesenchymal" tissues.
The major cell types derived from mesoderm are:
1. Fibroblasts
2. Mesothelium
3. Endothelium: forms the inner surface of vessels
4. Adipocytes
5. Myoblasts
6. Chondroblasts
7. Osteoblasts

Connective Tissue found throughout the body and is the most abundant and widely distributed in primary tissues. Furthermore, connective tissues have mesenchyme as their common tissue of origin, varying degrees of vascularity, nonliving extracellular matrix, consisting of ground substance and fibers.

A. Connective Tissues Elements:

All connective tissues share similar strucutral elements: a) Ground substance – unstructured material that fills the space between cells. b) Fibers – collagen, elastic, or reticular. d) Cells – fibroblasts, chondroblasts, osteoblasts, and hematopoietic stem cells. The basic component of many soft tissues or supporting structures is the substance collagen. Collagen is a protein that is woven from fibrils that give it both strength and resilience (the ability to bend or bounce back). In addition to collagen, connective tissues include reticulin fibers (seen in many solid organs such as liver) and elastic fibers (which contain the proteins elastin and fibrillin and have even more resilience than collagen). Connective tissues also contain a large amount of material that is extracellular. This material is called "ground substance". It provides much bulk to the tissues. Such ground substances include glycosaminoglycans such as hyaluronic acid, dermatan sulfate, and keratan sulfate. Intercellular materials can also include the fibronectin "glue" and supportive collagen fibers.
a) Ground Substance has:

- Interstitial (tissue) fluid
- Adhesion proteins – fibronectin and laminin

- Proteoglycans – glycosaminoglycans (GAGs)
- Functions as a molecular sieve through which nutrients diffuse between blood capillaries and cells

b) Fibers are:

- Collagen – tough; provides high tensile strength
- Elastic – long, thin fibers that allow for stretch
- Reticular – branched collagenous fibers that form delicate networks

Collagen fibers are most abundant protein in human body. Molecules of fibers are oriented to form a sort of lattice. As a result, these fibers are birefringent. These fibers are inelastic, but have great tensile strength. Thus, can be bent without breaking. While the fibers themselves do not stretch, their lattice-like arrangement can allow tissues containing the fibers to stretch to some extent. Thus, collagen fibers impart both strength and flexibility to tissue. Fibers often organized in parallel array forming a bundle. There are 5 types of collagen:

Type I - most common, found in every connective tissue.
Type II - found in hyaline and elastic cartilage and in vitreous body of eye.
Type III - found in reticular fibers, healing wounds, smooth muscle, and fetal skin.
Type IV - found in basal laminae of epithelia
Type V - found in placental basal laminae, tendon, and muscle sheaths.

d) Cells: Each Type of connective tissue has to be made by a certain cell type. In an immature stage each cell below secrets the fibers needed for its connective tissue.

Fibroblasts are the main and prototypic mesenchymal cell type that produces collagen fibers. Collagen, which exists in various subtypes, is the main component of connective tissue. Fibroblasts are slender, elongated cells with indistinct cytoplasmic borders and bipolar oval nuclei. Fibroblasts are sparsely distributed in between collagen fibers that support various epithelial tissues and other organs. With the exception of brain tissue, fibroblastic cell types can be found throughout the human body.

Chondrocytes are the main cell type in cartilage. Cartilage, similar to bone, is a specialized form of connective tissue. Cartilage is composed of a non-vascularized extracellular matrix of collagen fibers embedded in a gel-like proteoglycan matrix. Mature chondrocytes synthesize and secrete extracellular matrix, which separates the cells from each other and result in the appearance of isolated chondrocytes surrounded by a ***lacuna***.

Adipocytes are the main cell type in adipose tissue (fat). Adipose tissue is typically homogeneous and finely divided by faint septa. Adipose tissue is spread throughout the body and surrounds most organs and tissues in the human body. In the skin, underlying adipose tissue forms the subcutis as an integral component of the skin. Microscopically adipose tissue is mainly composed of ill-defined lobules of adipocytes surrounded by thin bands of collagen and small blood vessels. The cytoplasm of the adipocyte is compressed at the perimeter of the cell as it is displaced by a single lipid vacuole and only a thin rim of cell membrane is evident in the microscopic image. Adipocytes contain a small, thin and oval nucleus located peripheral to the dominating lipid vacuole, whereas nuclei of capillary endothelial cells are present at intersections between multiple adipocytes.

Osteoblasts: these cells can divide and form new cells. They produce the bone matrix and sit on the surface of the bone that is formed. The matrix is known as osteoid before it becomes calcified. Once calcified, the matrix consists mainly of hydroxyapatite crystal. Osteoblasts can produce new bone in response to an injury such as a fracture. Bone has also: ***Osteocytes:*** once an osteoblast becomes surrounded by matrix, sitting in a lacuna, it

transforms into an osteocyte. ***Osteoclasts*****:** these cells are derived from bone marrow stem cells and have a macrophage-like function. They sit within a Howship's lacuna on the surface of the bone.
Macrophages**:** many present in loose connective tissue. May look similar to fibroblasts; however, they are actively phagocytic and rounded in appearance. May be fixed in position (histocytes, phagocytes) or wandering.
Mesenchymal cells: embryonic connective tissue cells. Resemble fibroblasts, but usually smaller. In adults they are often found aggregated along capillaries where they are called pericytes (or perivascular cells). May differentiate into a number of connective tissue cell types when stimulated by an appropriate inducing factor.
Reticular cells: form three-dimensional networks of cells that are in contact via long processes. Form reticular fibers (type III collagen). This cellular network is called a cellular reticulum and forms the supportive framework for bone marrow, lymph nodes and the spleen. May be phagocytic. Also, may have a hemopoietic function as precursors for blood stem cells.
Mast cells*:* wandering cells that contain basophilic granules composed of heparin (a sulfated glycosaminoglycan), as well as other pharmacological agents such as histamine. Important in allergic reactions.
Plasma cells: antibody producing B-lymphocytes. As with other lymphocytes found in connective tissue and identifying feature is the spoke-like arrangement of the chromatin within the nucleus.
Leukocytes*:* various white blood cells.
Pigment cells (melanocytes*):* have shape similar to fibroblasts, but synthesize melanin that in the case of skin is transferred to other skin cells. As a result, these cells are not themselves generally pigmented. Originate from neural crest cells in embryo.

B. Types of Connective Tissue:

Besides bone, cartilage and blood all mature connective tissues belong to the Connective Tissue Proper class that can be divided into loose connective or dense connective.

1. Connective Tissue Proper: Loose

Areolar connective tissue:

- Gel-like matrix with all three connective tissue fibers
- Fibroblasts, macrophages, mast cells, and some white blood cells
- Wraps and cushions organs
- Widely distributed throughout the body

Adipose connective tissue:

- Matrix similar to areolar connective tissue with closely packed adipocytes
- Reserves food stores, insulates against heat loss, and supports and protects
- Found under skin, around kidneys, within abdomen, and in breasts
- Local fat deposits serve nutrient needs of highly active organs

Reticular connective tissue:

- Loose ground substance with reticular fibers
- Reticular cells lie in a fiber network
- Forms a soft internal skeleton, or stroma, that supports other cell types
- Found in lymph nodes, bone marrow, and the spleen

2. **Connective Tissue Proper: Dense Regular**

- Parallel collagen fibers with a few elastic fibers
- Major cell type is fibroblasts

- Attaches muscles to bone or to other muscles, and bone to bone
- Found in tendons, ligaments, and aponeuroses

3. **Connective Tissue Proper: Dense Irregular**
   - Irregularly arranged collagen fibers with some elastic fibers
   - Major cell type is fibroblasts
   - Withstands tension in many directions providing structural strength
   - Found in the dermis, submucosa of the digestive tract, and fibrous organ capsules

Connective Tissue: Cartilage

1. Hyaline cartilage
   - Amorphous, firm matrix with imperceptible network of collagen fibers
   - Chondrocytes lie in lacunae
   - Supports, reinforces, cushions, and resists compression
2. Elastic Cartilage
   - Similar to hyaline cartilage but with more elastic fibers
   - Maintains shape and structure while allowing flexibility
3. Fibrocartilage Cartilage
   - Matrix similar to hyaline cartilage but less firm with thick collagen fibers
   - Provides tensile strength and absorbs compression shock

Connective Tissue: Bone (Osseous Tissue)

- Hard, calcified matrix with collagen fibers found in bone
- Osteocytes are found in lacunae and are well vascularized
- Supports, protects, and provides levers for muscular action
- Stores calcium, minerals, and fat
- Marrow inside bones is the site of hematopoiesis

Connective Tissue: Blood

- Red and white cells in a fluid matrix (plasma)

Soft Tissues also include:

Tendons and Ligaments and Fascia: these tissues are mainly composed of collagen fibers that were made by fibroblasts. They are designed to have great tensile strength but be flexible. These tissues connect the bones and muscles. The fascia also provide support for adipose tissue and muscles.

Muscle: There are three types of muscle: skeletal muscle, cardiac muscle, and smooth muscle. The first two types are both forms of striated muscle.

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Introduction of Soft Tissue Tumor Pathology: Classification and Grading

Anastasia Nikolaidou
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Soft tissue tumors are a highly heterogeneous group of tumors that are classified by their line of differentiation, according to the adult tissue they resemble.

THE CLASSIFICATION OF SOFT TISSUE TUMOR

The classification of soft tissue tumors has changed a lot over the years. Earlier classification systems were based on the nuclear configurations. Terms like spindle cell sarcoma give little information about the nature and the malignant potential of a tumor. They are just descriptive. More current nomenclature is based on the line of differentiation of the tumor, that is the type of tissue formed by the tumor.

The classification system for tumors from W.H.O. is the most commonly used nomenclature today. It is useful for both clinical trials and research. The 2013 edition is a collective effort by pathologists from all over the world. One important addition from previous editions is the introduction of 2 new chapters (gastrointestinal stromal tumours and nerve sheath tumors).

There are also more details about cytogenetics and molecular features. Each histologic category is divided into a benign and a malignant group, but there are several tumors classified as being of intermediate malignancy. This term implies high rate of local recurrence and small risk of metastasis.

The most common soft tissue sarcomas in adults are the undifferentiated pleomorphic sarcoma (UPS) and liposarcoma (35%-45%) and among children Ewing sarcoma, neuroblastoma and rhabdomyosarcoma.

Benign soft tissue tumors outnumber malignant due to the fact that most of them don't need biopsy it is almost impossible to collect accurate data about them.

Malignant tumors are relatively rare, less than 1,5% of all cancers. The incidence changes with age. Children under 10 years have an annual incidence of 0,9/100.000. Adults over 70 years have an incidence of 18,2/100.000. The peak age is between 30 and 70 years.

GRADING SYSTEM

The histologic typing alone does not give enough information about the clinical course of a sarcoma. So, we must have some grading information, that is the degree of malignancy. Grading is based on evaluation of several histologic parameters.

The french system was developed by the French Federation of Cancer Centers Sarcoma Group (FNCLCC). A combination of cellular differentiation, mitotic index and extent of tumor necrosis was determined to be the most useful parameters for sarcoma grading. The principal

weakness of French system lies in the assignment of the differentiation score. Despite these issues, is still the most widely used grading system for sarcomas throughout the world. Despite the widespread use of some form of grading system in the diagnosis and management of sarcomas, experts agree that no grading system performs well on every type of sarcoma.

Therefore, the assignment of grade to many soft tissue tumors does not guarantee biologic equivalency to other sarcomas of comparable grade.

Referring to staging systems, several systems have been developed for soft tissue sarcomas in an attempt to predict prognosis.

The American Joint Committee on Cancer (A.J.C.C.) staging system is the most widely used.

TABLE1 Definitions of Grading Parameters for the FNCLCC System

Parameter	**Criterion**
Tumor Differentiation	
Score 1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas, synovial sarcomas, sarcoma of uncertain type
Mitotic Count	
Score 1	0-9/10 hpf
Score 2	10-19/10 hpf
Score 3	≥20/10 hpf
Tumor Necrosis (Microscopic)	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis
Histologic Grade	
Grade 1	Total score 2, 3
Grade 2	Total score 4, 5
Grade 3	Total score 6, 7, 8

TABLE 2 Tumor Differentiation Score According to Histologic Type in Updated FNCLCC System

Histologic Type	Tumor Differentiation Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma	2
MFH, pleomorphic type (patternless pleomorphic sarcoma)	3
Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS, with giant cells or inflammatory cells)	3
Conventional MPNST	2
Poorly differentiated MPNST	3
Malignant Triton tumor	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated/pleomorphic/epithelioid leiomyosarcoma	3
Biphasic/monophasic synovial sarcoma	3
Poorly differentiated synovial sarcoma	3
Rhabdomyosarcoma	3
Extraskeletal myxoid chondrosarcoma	2
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Ewing sarcoma/PNET	3
Epithelioid sarcoma	3
Malignant rhabdoid tumor	3
Undifferentiated (spindle cell and pleomorphic) sarcoma	3

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Immunohistochemical and Molecular Pathology in Diagnosis of Soft Tissue Tumours

Sotirios Sotiriou
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In recent years sophisticated and complex assays of molecular pathology (e.g. FISH, RT-PCR, NGS-based techniques, etc.) but also immunohistochemistry have been employed in the diagnosis of various neoplasms, including of course mesenchymal neoplasms such as soft tissue sarcomas (STSs)[1]. The utility of both molecular pathology assays and immunohistochemistry is not restricted only in the diagnosis (as diagnostic markers) but also provides crucial information regarding the prognosis and the risk stratification (as prognostic factors) and the response of the neoplasms in various therapeutic approaches (as predictive factors)[2,3].
In the case of STSs molecular pathology assays in particular and in a lesser degree immunohistochemistry has provided important information regarding the biological background of this rare and heterogeneous group of neoplasms. This deeper understanding of the biological background of STSs may result in a more advanced and detailed classification scheme which includes also entities characterized primarily by specific molecular events or even immunohistochemical expression of specific markers[1,4]. The idea of the molecular classification of STSs, similar to the molecular classification adopted in the case of other neoplasms such as leukemias is not a new idea[4].
To understand the trends and the rationale behind the molecular classification of STSs, as well as the strengths or the limitations that may impose we should attempt to answer three fundamental questions[4]:

1. What makes a group of STSs become a clinical entity?
2. Which should be the main driver of STS's classification (phenotype, genotype, clinical behaviour)?
3. How the classification of STSs is expected to evolve?

In order to answer these questions is necessary to highlight what is already known regarding the molecular biology of STSs. The study of three different categories of STSs may provide us with the helpful information in order to extract some conclusions:

1. STSs with the same molecular events but different morphology and clinical behavior
2. STSs with the same morphology but different molecular events and clinical behavior
3. STSs that can be diagnosed only based on a specific molecular event

STSs with the same molecular events but different morphology and clinical behavior: Some STSs share the same molecular events but have quite different morphology and clinical behavior. A characteristic example is the clear cell sarcoma of soft tissue and the angiomatoid fibrous histiocytoma. Both neoplasms can share (although in different frequency) the same molecular event, namely the translocation t(12;22)(q13;q12) which produce the fusion gene *EWSR1-ATF1* but they have quite different morphology and clinical behavior[2,5].

STSs with the same morphology but different molecular events and clinical behavior: The most common types of rhabdomyosarcomas are embryonal and alveolar rhabdomyosarcomas. Approximately 80% of alveolar rhabdomyosarcomas harbor a specific gene fusion, namely *PAX3-FOXO1* (≈60-70%) or less commonly *PAX7-FOXO1* (≈10-20%) and the remaining 20% are fusion-negative. Although fusion-positive and fusion-negative alveolar rhabdomyosarcomas are identical in terms of morphology they have a different molecular background and different clinical course with the fusion-positive cases having a more aggressive clinical course compared with the fusion-negative cases[2,5].

STSs that can be diagnosed only based on a specific molecular event: Probably the most characteristic example is that of the undifferentiated round cell sarcomas, a heterogeneous group of sarcomas that shares quite a similar morphology. In recent years two new entities emerged from this group of sarcomas which are characterized by a specific molecular event, namely the CIC-rearranged and the BCOR-rearranged sarcomas, and can be diagnosed only in the presence of this specific molecular[2,4].

In conclusion, one can argue that “tumors are much more than the morphology they have” but also they are “much more than the immunophenotype they have” and “much more than the mutations they harbor”. Both molecular pathology assays and immunohistochemistry are extremely important tools in the arsenal of the pathologists that can provide them with crucial information regarding the diagnosis or even the prognosis and/or the response of the neoplasm in various therapeutic approaches[1–3]. Although a clear and strict answer to the question of “What makes a group of STSs become a clinical entity?” may not be available, one can argue that at least a differentiation in terms of the phenotype (morphology and immunophenotype), and/or the genotype (molecular background) and/or the clinical behavior from other STSs is necessary to argue for a distinct clinical entity. From these three parameters, the differentiation in clinical behavior holds probably the most important place since it determines to a large degree the necessity of a more aggressive therapeutic approach or a closer follow-up of the patient. In the same line of thought, phenotype (morphological variants and immunophenotype) and/or genotype (molecular events) related to a specific clinical behavior (e.g. worst or best prognosis, response to a specific therapeutic approach, etc.) holds an equally important place. Therefore, the classification of STSs is expected to evolve in a way where parameters such as phenotype (morphology and immunophenotype) but also genotype (molecular background) will need to be taken into consideration with emphasis on any crucial information regarding the clinical behaviour of the disease (here STS). Both immunohistochemistry and even most importantly molecular pathology assays provide the scientific community and the pathologists with crucial information regarding the biological background of STSs resulting in a deeper and more comprehensive understanding of the nature of this rare and heterogeneous group of neoplasms. In this line of reasoning, the molecular classification of STSs is expected to be an essential part of the classification of STSs.

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Gastrointestinal Stromal Tumours: Histology and genetics.

George Agrogiannis
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1st PART – Histology and diagnosis

Historical review

In the 1940s stromal tumors arising in the GI tract were generally regarded as smooth-muscle neoplasms (using the terms “leiomyoma,” “leiomyosarcoma,” “leiomyoblastoma,” and “bizarre leiomyoma”) until at least the late 60s.

The application of electron microscopy in the late 60s revealed that relatively few of these neoplasms showed convincing ultrastructural evidence of smooth-muscle differentiation. With the introduction of immunohistochemistry in the early 80s, it was also soon appreciated that many of these lesions lacked the immunophenotypic features of smooth-muscle differentiation, and this led Mazur and Clark in 1983 to introduce the more generic designation “stromal tumor.”

A subset of such lesions that showed clear ultrastructural evidence of autonomic neuronal differentiation was designated “plexosarcoma” by Herrera et al in 1984 and subsequently became better known as gastrointestinal autonomic nerve tumors (GANTs).

It is now appreciated that KIT immunoreactivity, in the specific context of mesenchymal lesions of the GI tract, defines a group of tumors showing differentiation toward interstitial cells of Cajal. The identification of KIT gene mutations in the majority of GIST has given GIST added importance because it has become a paradigm for targeted therapy of oncogenic proteins in solid tumors.

Localization

They are found along the entire length of the digestive tract but are most common in the stomach (40-70%), small intestine (20-40%) and colon and rectum (5-15%). GISTs also rarely involve the esophagus, appendix, and gall bladder.

Epidemiology

GISTs are the most common clinically significant mesenchymal neoplasm of the GI tract. Population-based studies estimate the annual incidence at 10 cases per million. These GISTs are clinically significant GISTs of greater than 2 cm in size that require surgical evaluation and potentially systemic therapy. MicroGISTs, less than 1 cm in diameter, are quite common. Autopsy studies have identified microGISTs, in up to 22.5% of patients.

They arise over a wide age range, from children to the elderly with a peak median age of 64 years at the time of diagnosis. They occur with an approximately equal sex predilection (47.3% female; 52.7% male), except in children, where there is a clear female predominance.

No etiologic factors related to GIST have been identified and although the vast majority of GISTs occur as sporadic tumors with somatic mutations, GISTs also occur rarely in various tumor syndromes.

Macroscopic findings

Macroscopically, GISTs show many faces ranging from small ones with uniform appearance, to larger tumours with heterogenous appearance, solid or hemorrhagic. Others

present with necrotic areas, or, finally, they maybe very large tumours attached to the bowel and expanding to the abdominal wall.

GISTs have a characteristic pattern of metastasis: they do not metastasize to lymph nodes, they are sarcomas after all (there is one exception though). They metastasize to the liver or throughout the peritoneal cavity as numerous metastatic nodules. It is unusual for GIST to metastasize outside of the abdomen. Dermal, subcutaneous, bone, brain, and lung metastases occur very rarely.

Histological findings

The lesions vary in their cellularity, ranging from low, to intermediate, to high.
They may also contain nests of epithelioid cells with abundant eosinophilic cytoplasm and areas of myxoid stroma. Hypocellular GISTs with hyalinized stroma are also described, while some tumors show nuclear palisading, or paranuclear vacuolization.

Finally, dedifferentiated GIST demonstrate areas of pleomorphic cells, they contain atypical mitotic figures, and include large bizarre cells. In this case, immunohistochemistry for KIT is positive in the well-differentiated GIST and negative in the dedifferentiated component.

Regarding the immunoreactivity in gastrointestinal stromal tumors, cytoplasmic pattern for KIT B, dot-like or membranous pattern are all common. For DOG1 expression, the membranous staining pattern is typical.

Diagnosis

At first, the morphology should be consistent with that of a GIST. Second, if IHC staining for c-Kit is positive, then the tumor can be diagnosed as GIST. If the KIT stain is negative but DOG1 is positive, the tumor can be diagnosed as GIST. Gastrointestinal mesenchymal tumors that harbor a KIT or PDGFRA mutation can also be diagnosed as GIST, even though they are negative for both KIT and DOG1.

The risk of recurrence is predicted by location, size and the number of mitoses. The main cut off points are 2-5 cm for the size and 5 mitoses per 50 HPF for the mitotic activity. The prognosis is different when the tumor is located in different anatomical sites. Interestingly the relative risk increases as we go lower in the GI tract. Also, the small lesions under 2 cm with low mitotic activity are considered benign.

2nd PART – Molecular findings and genetics

Understanding underlying mutations in GISTs is critical for the diagnosis and patient care and these are tumours with quite well defined molecular alterations which reflects to the targeted therapy. Imatinib is the mostly used drug agent for the therapy of GISTs.

KIT mutations

KIT mutations cause activation of the tyrosine kinase receptor pathway. Four different regions of KIT, namely exon 9, exon 11, exon 13, and exon 17, are most often mutated in sporadic GISTs. Most KIT mutations (nearly 67%) involve the juxtamembrane domain (exon 11), followed by extracellular domain (exon 9). Very rarely, mutations have been found in other exons.

Exon 11 mutations most commonly are composed of deletions of one or more codons; some of these (codons 557–558) are typically associated with poor clinical outcome. Missense point mutations are the next most common type of mutations. In gastric GISTs, these mutations are associated with a better prognosis; no such correlation has been documented with small intestinal GISTs. Virtually all exon 9 mutations are characterized by a

6- nucleotide duplication These mutations are associated with small intestinal GISTs and a worse prognosis. Exon 13 and 17 mutations are very rare and are usually substitutions. Exon 13 mutations are mostly found in gastric GISTs, while exon 17 occur predominantly in small intestinal GISTs, and do not appear to have any prognostic implication

PDGFRA mutations

PDGFRA is receptor tyrosine kinase, and similar to KIT, activating mutations cause downstream activation of multiple cell-signaling cascades that control cellular functions. Exon 18, exon 12, and exon 14 are the 3 PDGFRA regions that are mutated in GISTs. Overall, nearly 7% of GISTs harbor PDGFRA mutations.

More than 80% of those mutations are missense D842V mutations in exon 18. They have a strong predilection for either gastric or extraabdominal locations, exhibit an epithelioid phenotype, and they show no response to imatinib. PDGFRA-mutant GISTs tend to be faintly almost completely negative for KIT by immunohistochemistry.

Wild Type GISTs

Fifteen (15) percent of the tumors do not harbor either the KIT or PDGFRA mutations and they are designated as Wild Type GISTs. WT GISTs in particular remain a challenge as they are generally resistant to imatinib. Based on studies, we know now that other molecular alterations are responsible for these tumours. These include SDH-deficient GISTs, BRAF/RAS mutated and those harboring NF-1 mutations.

SDH deficient GISTs

SDH is an enzyme complex located within the mitochondrial membrane that participates in the Krebs cycle. The complex consists of 4 subunits SDHA, SDHB, SDHC, SDHD. SDH deficiency leads to accumulation of succinate which is toxic for dioxygenase ten-eleven translocation (TET) and histone lysine demethylases (KDM) which leads to oncogene activation and tumour suppression inactivation. Additionally SDH deficiency leads to inhibition of profyl hydroxylases of HIF1-a leading to activation of the HIF1a.

These GISTs are usually located in the stomach, the have a multinodular appearance and they are C-KIT, DOG-1 positive. SDH-B staining is negative, regardless of the deficient subunit. They exhibit aggressive features, such as lymphovascular invasion, lymph node metastasis, liver – peritoneal involvement but they show indolent course.

Quadruple GISTs

A subset of GISTs lack mutations in the KIT/PDGFRA or RAS pathways and yet retain an intact SDH complex. It was proposed that these tumors could be designated as quadruple wild-type (WT) GIST. The pathogenesis and underlying biology of quadruple WT GISTs is currently unknown. Moreover, descriptive clinical and pathological data for this group have not been defined yet. Further molecular and clinicopathological characterization of quadruple WT GIST will help to determine their prognosis as well as assist in the optimization of medical management.

BRAF mutations

Among the adult GISTs that are wildtype for KIT and PDGFRA, a small subset are driven by mutations in the gene for BRAF. Activated BRAF protein acts through the MAPK pathway: RAS/RAF/MEK/ERK. This actually is one of the pathways activated by KIT and PDGFRA, but BRAF activates this path at a later point in the signaling sequence without stimulation by KIT or PDGFRA. The MAPK pathway is involved in cell proliferation, migration, and survival. These tumours (very few cases are reported so far) exhibit spindle cell morphology and dot like expression of BRAF V600E antibody.

Syndromic GISTs

Carney – Stratakis syndrome related GISTs carry germline mutations in SDHB, SDHC, or SDHD. They are multifocal GISTs combined with paragangliomas, and pheochromocytomas. They tend to be localized to the stomach with epithelioid morphology, slow growth but they also frequently metastasize (especially to lymph nodes). Their response to imatinib is poor and their clinical behavior is unpredictable and there appears to be no correlation between conventional risk assessment and clinical behavior.

Carney triad related GISTs are sporadic sporadic and found in young women along with paraganglioma, and pulmonary chondroma. Carney triad associated GISTs are pathologically and clinically different from sporadic GISTs. These lesions tend to exhibit an epithelioid morphology and appear to be at a higher risk for metastasis, particularly to lymph nodes.

Germline mutations in KIT and PDGFRA have been documented. Every family member who harbors a germline KIT mutation will develop one or more GISTs, usually at a younger age than those with sporadic tumors. Clinically, many members of familial GIST present cutaneous findings that include hyperpigmentation (especially perineal), increased numbers of nevi, and systemic mastocytosis. Morphologically, these tumors are indistinguishable from sporadic GISTs. Although some reports suggest that these tumors appear to be indolent, in a study 2 patients presented with metastases at the time of diagnosis despite having variable mitotic activity.

Multiple GISTs also arise in the setting of neurofibromatosis type I (NFI). This syndrome results from germline mutation of the NF1 gene. Approximately 7% of patients with NF1 have GISTs.68 NF1-related GISTs most commonly occur as multiple small tumors in the small bowel and exhibit spindle cell morphology. Most of these tumors do not harbor the KIT or PDGFRA mutations. They do, however, express KIT; a subset of them also show S100 immunoreactivity. Clinically, they usually exhibit a benign behavior; rare cases of malignant GISTs associated with numerous benign tumor nodules have been reported.

Pediatric GISTs

GISTs are exceedingly rare tumors in the pediatric population. Pediatric GISTs usually present during the second decade of life, the median age of presentation being 13 and 14.5 years. They have a marked female predominance, are commonly located in the stomach, and most often display an epithelioid morphology. The presence of multiple tumor foci is another distinctive feature of pediatric GISTs. Pediatric KIT-wild-type GISTs exhibit KIT activation at levels comparable with KIT mutant pediatric and adult GISTs, although they do not have KIT or PDGFRA mutations. A subset of patients with pediatric GIST have Carney-triad, and therefore, GIST in a child should trigger evaluation for potential Carney triad. In general, these GISTs follow an indolent course.

Precursor lesions

These lesions have been variably designated as sporadic Cajal cell hyperplasia, microscopic GISTs, GIST tumorlets, or ‘‘seedling’’ GISTs. Microscopic foci of KIT-positive spindle cell hyperplasia are commonly found in patients with germline KIT or PDGFRA mutations or NF1 mutations. They have also been described adjacent to sporadic GISTs. They are common incidental findings in gastroesophageal resections (9%–35%). Nearly 85% harbor KIT mutations but only a small proportion (0,1%) progress to clinically significant GISTs. Therefore, these microscopic lesions require additional genetic events to transform into clinically significant neoplasms. These include 14q deletion, 22q deletion, 1p deletion, 8p gain, 11p deletion, 9p deletion, and 17q gain. Indeed, the accumulation of molecular alterations is now believed that triggers the progression from microGISTs to high risk GISTs.

Conclusion

GISTs demonstrate diverse clinical profiles in that they can arise in any part of the GI tract and can present as tumours ranging from incidental microscopic tumours to those that follow a malignant and life – threatening course by metastasis. This diversity is also reflected in the oncogenic events that lead to their development. Although most GISTs can be risk-stratified using conventional parameters of size, location and mitotic activity, the current knowledge about molecular alterations in these tumours suggests that perhaps incorporating mutational status is even more important for providing accurate information regarding prognosis and treating advanced tumours using pathway specific inhibitors.

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Vascular Tumors

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A general classification of vascular tumors is shown in [Table 1]. Features of benign vascular tumors include a lobular architecture, well-formed vessels, and a single layer of endothelial cells. Features that suggest malignancy include a dissecting growth pattern, an infiltrative margin, complex anastomosing vascular channels, cytologic atypia and endothelial multilayering, as well as absence of a well-defined layer of peucytes. Mitoses and cellularity are not discriminatory in this regard, in this regard. A single atypical feature is generally insufficient for a diagnosis of malignancy. Most vascular tumors are vasoformative and are readily recognized as being vascular. Less commonly, vascular tumors are predominantly spindled.

Vasoformative tumors are particularly common in the skin, where most are benign. Some benign vasoformative tumors merit consideration because they may be diagnostically challenging. Papillary endothelial hyperplasia typically arises in a normal vessel (primary), a preexisting vascular lesion (secondary) or a hematoma (extravascular). The characteristic hyalinized papillae are helpful on recognition if the surroundings vessel wall is not visible. Reactive angioendotheliomatosis usually affects adults with an underlying systemic disease, the clinical presentation being often dramatic. Histologic patterns are quite variable, including capillary-like, tufted angioma-like and less often, angiosarcoma-like vascular proliferation. This histological variation, in association with the clinical features, constitutes the main diagnostic clues. Glomeruloid hemangioma occurs in patients with POEMS syndrome. Key features are intravascular glomeruloid tufts and intracytoplasmic hyaline globules. Papillary hemangioma is similar but occurs in healthy patients and has well-developed intravascular papillae. Sinusoidal hemangioma has a propensity to arise in mammary subcutaneous tissue where it may mimic a well-differentiated angiosarcoma. It is composed of widely dilated “sinusoids” in a back-to-back arrangement separated formation of pseudopapillary structures being common. In the presence of focal endothelial multilayering, multifocal infiltration of adjacent breast parenchyma and diffuse mild endothelial atypia, the diagnosis of well-differentiated mammary angiosarcoma should be rendered. Acquired progressive lymphangioma features multiple thin-walled anastomosing channels dissecting around dermal collagen bundles and adneal structures, closely, simulating angiosarcoma, although it lacks significant cytologic atypia, endothelial multilayering and mitotic activity. Clinical presentation and HHV-8 immunostaining may allow the distinction from lymphangioma – like Kaposi sarcoma. Post radiation atypical vascular lesion may be histologically identical but can be distinguished by clinical correlation. Verrucous hemangioma and tufted angioma are rare variants of capillary hemangioma that present in childhood. The superficial potion of the former resembles angiokeratoma, but the capillary proliferation extends into the deep dermis. Tufted angioma is to be distinguished from Kaposi, form hemangio, endothelioma [Table 2].

Classification of Vascular Tumors of Skin and Soft Tissue

Vascular Ectasias

- Spider angioma
- Venous lake
- Hereditary hemorrhagic telangiectasia
- Angioma serpiginosum
- Angiokeratoma
- Port-wine stain[a]

Reactive Vascular Proliferations

- Papillary endothelial hyperplasia (Masson tumor)
- Bacillary angiomatosis
- Reactive angioendotheliomatosis
- Glomeruloid hemangioma
- Acroangiodermatitis (pseudo-Kaposi sarcoma)

Benign Vascular Tumors/Malformations[b]

- Capillary hemangiomas
- Juvenile capillary hemangioma
- Lobular capillary hemangioma (pyogenic granuloma)
- Verrucous hemangioma
- Cherry angioma
- Cavernous hemangioma/venous malformation
- Sinusoidal hemangioma
- Arteriovenous hemangioma (cirsoid aneurysm)
- Microvenular hemangioma
- Hobnail hemangioma (targetoid hemosiderotic hemangioma)
- **Spindle cell hemangioma**
- *Epithelioid hemangioma (including angiolymphoid hyperplasia with eosinophilia)*
- *Epithelioid angiomatous nodule*
- Tufted angioma
- Cavernous lymphangioma/lymphangioma circumscriptum/lymphatic malformation

- Acquired progressive lymphangioma (benign lymphangioendothelioma)
- Glomuvenous malformation
- Arteriovenous malformation
- Deep (e.g., intramuscular, synovial) vascular malformations (usually mixed vessel-type)
- Angiomatosis/lymphangiomatosis

Intermediate (Locally Aggressive or Rarely Metastasizing) Vascular Tumors

- **Kaposiform hemangioendothelioma**
- Papillary intralymphatic angioendothelioma
- Retiform hemangioendothelioma
- Composite hemangioendothelioma
- **Pseudomyogenic hemangioendothelioma** (see Chapters 3 and 15)
- **Kaposi sarcoma**[c]

Malignant Vascular Tumors

- *Epithelioid hemangioendothelioma*
- Angiosarcoma
- *Epithelioid angiosarcoma*
- **Spindle cell angiosarcoma**

Tumors in bold are often predominantly spindled; tumors in italics are often predominantly epithelioid; the remainder are vasoformative.

Table 1: "Practical Soft Tissue Pathology", Jason L. Hornick

	Kaposi Sarcoma (Nodular Stage)	Kaposiform Hemangioendothelioma	Tufted Angioma
Age	Adults	Infants and young children	Children
Site	Distal extremities (rarely disseminated)	Retroperitoneum, extremities > other	Neck/upper trunk > extremities
Depth	Cutaneous	Deep soft tissue > superficial	Cutaneous; infrequent subcutaneous extension
Architecture	Typically a single circumscribed nodule	Ill-defined coalescing lobules	Small, discrete lobules
Spindle cell component	Predominant	Predominant	Absent or only focal at periphery of lobules
Vascular spaces	Slitlike	Slitlike	Rounded
Characteristic features	Lymphoplasmacytic infiltrate	Glomeruloid clusters of epithelioid cells	Dilated crescentic lymphatics at periphery of lobules

Table 2: "Practical Soft Tissue Pathology", Jason L. Hornick

Symplastic hemangioma is a recently described hemangioma variant characterized by degenerative nuclear atypia restricted to the vascular smooth muscle and stromal cells of an otherwise banal hemangioma. Microvenular hemangioma displays irregularly branching compressed venules within a sclerotic reticular dermis, which retain pericytic layer and tend to involve arrector pili muscle. The lesion may be confused with patch-stage Kaposi sarcoma which, however, displays a spindle cell component and HHV-8 immunoreactivity.
A number of vasoformative lesions, either benign of intermediate, are typified by the presence of **hobnail cells**. Their features are summarized in [Table 3]. Hobnail hemangioma and papillary intralymphotic angioendothelioma express lymphatic endothelium associated markers. Most of hobnail hemangioma cases lack the classic targetoid clinical appearance and are characterized by a biphasic pattern with hobnail endothelial cells limited to the dilated superficial vessels. Atypical post radiation vascular lesion can be histologically similar. Prominent intravascular papillary formation within dilated lymphatic spaces is characteristic of papillary intraymphatic angioendothelioma and elongated narrow vascular channels with focal papillary formation and focal solid-appearing areas characterize retiform hemangioendothelioma.

	Hobnail Hemangioma	Papillary Intralymphatic Angioendothelioma (Dabska Tumor)	Retiform Hemangioendothelioma	Postradiation Atypical Vascular Lesion
Age	Young adults	Infants and children	Young adults	Older adults
Anatomic sites	Trunk, extremities	Wide anatomic distribution	Extremities	Any site of previous radiation (breast most common)
Depth	Dermis	Subcutis and often reticular dermis	Dermis and occasionally subcutis	Dermis
Vascular pattern	Biphasic, with dilated superficial vessels and compressed deep vessels	Cavernous, lymphangioma-like spaces with intraluminal papillae	Narrow, anastomosing channels	Variable, but often ectatic superficially; can be biphasic
Endothelial cells	Hobnail superficially, flattened deep	Flattened to hobnail	Hobnail	Flattened to hobnail
Occasional features	Small intraluminal papillae	Associated lymphatic malformation	Small intraluminal papillae	Small intraluminal papillae
Associated findings	Hemosiderin, mild lymphocytic infiltrate	Prominent lymphocytic infiltrate	Prominent lymphocytic infiltrate, hemosiderin	Patchy lymphocytic infiltrate
Margins	Symmetric, wedge shaped	Ill defined	Infiltrative	May be wedge shaped

Table 3: "Practical Soft Tissue Pathology", Jason L. Hornick

Angiosarcoma may arise in the skin, deep soft tissues or breast parenchyma. Cutaneous angiosarcoma may be sporadic or associated with chronic lymphedema or radiation therapy. Secondary cutaneous angiosarcoma regularly shows amplification of MYC with consequent MYC immunoreactivity, whereas primary angiosarcoma rarely does so. Post radiation atypical vascular lesion is negative for MYC immunohistochemically. Mammary angiosarcoma is rarely primary and more often secondary due to radiation therapy for breast carcinoma. Histology may be deceptively bland in low-grade forms, the most helpful clues being infiltrative architecture, focal endothelial multilayering and diffuse endothelial cell atypia.. Prognosis is uniformly poor regardless of grade.

The endothelial nature of **epithelioid** vascular tumors [Table 4] may not be readily apparent on histologic sections which prompt the differential diagnosis from epithelioid sarcoma and metastatic carcinoma. Keratin expression in a minority of epithelioid vascular tumors adds to the risk of misinterpretation.

	Epithelioid Hemangioma	Epithelioid Angiomatous Nodule	Epithelioid Hemangioendothelioma[a]	Epithelioid Angiosarcoma
Architecture	Well-formed vessels predominate; focal cordlike or solid areas	Exophytic nodule; solid sheet of endothelial cells	Cords, strands, and single cells	Solid sheets, cleftlike spaces, and large, irregular vascular channels
Margins	Circumscribed	Circumscribed	Infiltrative	At least focally infiltrative
Cell shape	Cuboidal to hobnail	Plump, polygonal	Plump polygonal, oval, or stellate	Plump, polygonal
Cytoplasm	Eosinophilic to amphophilic	Eosinophilic to amphophilic	Pale pink, glassy	Eosinophilic to amphophilic
Intracytoplasmic vacuoles	Occasional	Occasional	Frequent	Variable
Inflammatory infiltrate	Prominent	Mild to moderate	Absent	Variable
Nuclear atypia	Absent to mild	Absent to mild	Mild to moderate	Moderate to severe
Mitotic figures	Rare	Variable	Rare/infrequent	Frequent

Table 4: "Practical Soft Tissue Pathology", Jason L. Hornick

Although epithelioid hemangioma is predominantly vasoformative solid or sheet like areas may be present and in some cases may predominant ("cellular epithelioid hemangioma"). Most cases have a prominent lymphocytic and eosinophilic inflitrate which however, is not required for the diagnosis. A small proportion of cases arise in deep soft tissue, bone, oral mucosa and penis. The tumor is often multifocal at presentation. FOS and FOSB rearrangements are found in a large subset of epithelioid hemangiomas which show nuclear FOSB immunoreactivity. Epithelioid angiomatous nodule is a recently described benign vascular lesion which overlaps with epithelioid hemangioma from which it is distinguished by being circumscribed, located in the superficial dermis, associated with epidermal hyperplasia and displaying a solid architecture. Epithelioid hemangioendothelioma is a low-grade vascular sarcoma characterized by myxohyaline stroma, cells with glassy pink cytoplasm and intracytoplasmic vacuoles, and absence of well-formed vessels. CAMTA1 fusions are found in 85-90% of cases resulting in nuclear expression of CAMTA1, whereas small subsets (5%) of cases with more obvious vasoformative architecture harbor YAP1-TFE3 fusions. Histologic features associated with a more aggressive behavior include frequent mitoses, significant nuclear atypia, necrosis or solid sheet-like areas. Epithelioid angiosarcoma is very uncommon in the skin and mammary parenchyma and predominates in deep soft tissues, and visceral sites. It usually shows a solid or nested architecture simulating a carcinoma. Keratin expression is common (30-50% of cases). The differential diagnosis is broad and includes

carcinoma, epithelioid sarcoma, melanoma, epithelioid MPNST and anaplastic lymphoma. Immunohistochemistry for endothelial antigens is invaluable in such cases.
A number of vascular tumors are dominated by **spindle cell histology.** The classical features of spindle cell hemangioma are cavernous vascular spaces, solid spindled areas composed of fibroblasts and a smaller population of pericytes, and vacuolated endothelial cells. Tumors are frequently multifocal but clinically benign. More than half of the cases have an intravascular component. Somatic mutations of IDH1 or IDH2 have been identified in both sporadic and syndromic (i.e. associated with Maffucci's syndrome) cases. Kaposiform hemangioendothelioma is discussed in [Table 2]. Kaposi sarcoma is a multifocal HHV-8 associated vascular proliferation occurring in classic African endemic, iatrogenic and epidemic clinical settings. Three clinical/historic stages are recognized – patch, plaque, modular dermal. Microscopy shows well-formed irregular vascular channels dissecting collagen fibers and spindled endothelial cells in varying properties, depending on the stage, with patch stage displaying a vasoformative histology as compared to the nodular stage which is a spindled cell lesion. A high degree of suspicion is required to render the diagnosis in the patch stage in those rare cases with a lymphangioma-like histology. Immunostaining for HHV-8(LANA) is very helpful to confirm the diagnosis in difficult cases. Spindle cell angiosarcoma may be reminiscent of nodular Kaposi sarcoma or fibrosarcoma. The presence of well-formed vascular channels focally may betray the vascular nature of the tumor but immunohistochemistry is required for confirmation. Pseudomyogenic hemangioendothelioma is a spindle cell vascular neoplasm of intermediate biologic potential usually multifocal at presentation. It usually affects young males. Histology is that of an infiltrative spindle cell fascicular neoplasm with eosinophilic myoid-like cytoplasm, vesicular nuclei, mild nuclear atypia and often prominent stromal neutrophils. The neoplastic cells are positive for keratin, AE1/AE3, Fli-1, ERG and FOSB and maybe negative to other endothelial markers.

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An approach of epithelioid soft tissue tumors

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Epithelioid cell morphology is defined as large polygonal cells with round nuclei and prominent well-defined cytoplasm, mimicking carcinoma cells. This appearance may be associated (as in epithelioid sarcoma) or not associated (as in most other epithelioid soft tissue tumors- ESTTs) with phenotypic and ultrastructural features of true epithelial differentiation. As a highly heterogeneous group, epithelioid cell tumors present significant morphological and phenotypic overlaps, sometimes making their differential diagnosis especially broad. A majority of these neoplasms driven by switch/sucrose non-fermenting (SWI/SNF) complex inactivation express vimentin and pankeratins irrespective of their histogenetic subtype, location and the SWI/SNF gene affected. Some malignant ESTTs may display predominantly or pure rhabdoid morphology so that their recognition and distinction from rhabdoid variants of carcinoma and melanoma, without counting on demographic and topographic features, could occasionally be very difficult.
Myoepithelial tumors (myoepithelioma and myoepithelial carcinoma) of soft tissues present with variable epithelioid morphology. Myoepithelial carcinomas are frequently characterized by prominent lobulation and variably myxoid stroma. Neoplasms with *EWSR1-POU5F1* gene fusions tend to feature prominent nested epithelioid morphology. Immunohistochemically, there is variable staining for keratin, EMA, S100, SOX10, GFAP and p63. INI1 expression is lost in nearly half of cases, secondary to loss on chromosome 22q. Half of myoepithelial soft tissue tumors are associated with *EWSR1* rearrangements to a range of fusion partners or variant *FUS* fusions.
Epithelioid haemangioma (EH) is a benign vascular neoplasm with well-formed vessels, lined by plump, epithelioid endothelial cells. Subcutaneous EH is usually associated with a small artery and when there is circumscription and peripheral lymphoid reaction with follicles, it may be confused with lymph nodes. Immunostaining for SMA highlights an intact pericytic layer around vessels and ERG and CD31 highlight the epithelioid vascular cells. Focal expression of cytokeratin may be observed. Since FOSB rearrangements are present in EH, FOSB immunohistochemical expression is shown in 54-100% of EHs.
Ossifying fibromyxoid tumor (OFT) is characterized by uniform epithelioid cells within a background of fibromyxoid stroma. Tumor cells may express S100 and desmin. INI1 expression is lost. OFT is associated with fusions often involving PHF1.
Epithelioid hemangioendothelioma (EHE) is a frequently angiocentric tumor, comprised of round and polygonal cells with mild nuclear atypia, often set in a background of myxohyaline. EHE is positive for vascular markers (ERG, CD31, CD34) but also up to one third of tumors express EMA and keratin. Since EHE harbors CAMTA1-WWTR1 fusion, a strong nuclear immunohistochemical expression of CAMTA1 is expected. The latter distinguishes EHE from epithelioid sarcoma and epithelioid angiosarcoma. Distinction between EHE and epithelioid angiosarcoma is important, as the former shows 20-30% metastatic risk and the latter is very aggressive with high rates of tumor-related death. A subset of EHE having YAP1-TFE3 fusion is positive for TFE3.
Epithelioid sarcoma (ES) is classified into classical(distal) and proximal subtypes. Both subtypes show epithelioid and polygonal cells having round nuclei, prominent nucleoli and

dense cytoplasm with distinct borders. The tumor cells are arranged into lobules or nodules with frequent central palisaded necrosis, an appearance reminiscent of granuloma-like process. This is why classical ES can be misclassified as a benign granulomatous or reactive lesion. Classical distal-type ES typically arises in the distal extremities in teens and young adults. Proximal-type ES, which usually presents in the proximal limb girdles of older adults, is comprised of anaplastic-looking epithelioid, occasionally rhabdoid, cells with high-grade nuclear features, thus mimicking anaplastic carcinoma, melanoma, anaplastic lymphoma or sarcoma. ES expresses typically immunohistochemically EMA and keratin; there is loss of nuclear expression of INI1, secondary to *SMARCB1* alterations. CD34 is positive in 50% of cases. When ERG is positive, it has to be distinguished from epithelioid vascular tumors. If keratin is expressed, it should not point to carcinoma, given the fact that ES is one of the few sarcomas that metastasizes to lymph nodes. INI1 loss is expressed not only by ES but also by malignant rhabdoid tumor, renal medullary carcinoma and soft tissue myoepithelial tumors. The controversial differential "proximal rhabdoid ES versus malignant rhabdoid tumor" can be solved mainly based on clinical and demographic features rather than morphology.

Extraskeletal myxoid chondrosarcoma (EMC) is composed of uniform round or ovoid cells, (arranged either singly or in clusters or in cords) within myxoid stroma. There is no evidence of cartilaginous differentiation. Immunohistochemically, up to 50% show focal S100 positivity. INI1 expression is lost in a subset of cases secondary to EWSR1 rearrangements. EMC harbors gene fusions involving NR4A3, often partnered with EWSR1.

Clear cell sarcoma of soft tissue (CCS)

It is composed of uniform epithelioid cells and prominent nucleoli. CCS harbors *EWSR1-ATF1* and *EWSR1-CREB1* fusions and expresses S-100 and HMB-45; melanoma has to be excluded in older patients.

Malignant rhabdoid tumor

These rare and highly aggressive tumors present either in the central nervous system as pediatric central atypical teratoid/rhabdoid tumors (AT/RT) or as non-central (renal and extrarenal) malignant rhabdoid tumors (MRT). Given the frequent presence of germline SWI/SNF mutations, it is often difficult to discriminate between independent multifocal disease versus metastases in individuals. MRT coexpresses LMWCK and Vimentin, similar to epithelioid sarcoma. 98% of MRT is driven by SMARCB1 inactivation.

SMARCA4-deficient thoracopulmonary and uterine sarcoma

A highly aggressive ovarian malignancy in girls and young adult women is the small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). SMARCA4 loss has been recognized as an underlying mechanism in a variety of highly aggressive large cell epithelioid malignancies indistinguishable from SCCOHT. Large cell anaplastic malignant neoplasms, reported recently as BAF-related mediastinal neoplasms (sarcoma), are highly aggressive neoplasms affecting predominantly young adult males who have a smoking history. Based on demographic, clinicopathological and genetic features of the disease and its association with rhabdoid tumor predisposition syndrome, it has been questioned whether SCCOHT is a true epithelial malignant tumor or a visceral variant of malignant rhabdoid tumors.

Epithelioid malignant peripheral nerve sheath tumor

It is composed of large monomorphic epithelioid cells with central macronucleoli, features that usually represent a difficult differential with proximal-type epithelioid sarcomas. Immunoreactivity for S100 and SOX10 allows the distinction between MRT and epithelioid sarcoma. Loss of SMARCB1 expression as a result of inactivating mutations is observed in 70% of epithelioid MPNSTs and in 40% of epithelioid schwannomas.

Sclerosing epithelioid fibrosarcoma (SEF)
It is an aggressive soft tissue malignant tumor composed of medium to large epithelioid fibroblasts, arranged in cords and nests in a densely sclerotic hyalinized stroma. The morphology described is reminiscent of metastatic carcinoma or extraskeletal osteosarcoma if prominent osteoid-like sclerosis is present. Immunohistochemistry: vimentin, CD99, bcl2, MUC4.
MUC4-negative sclerosing epithelioid fibrosarcoma
Its morphological features are highly overlapping with SEF or with hybrid SEF/LGFMS with recurrent *KMT2A/YAP1* gene fusions.
TFE-3 rearranged epithelioid soft tissue neoplasms
Alveolar soft part sarcoma (ASPS) and **a subset of PEComa** are the major members of this group of rare neoplasms that present a large cell epithelioid "moderately eosinophilic or clear" morphology. ASPS is an aggressive malignant neoplasm, prone to disseminate, in contrast to PEComas which are benign rarely metastasizing neoplasms, except for malignant PEComa. Immunohistochemically, PEComas express melanocytic and smooth-muscle markers. ASPS doesn't express these markers, except for desmin rarely. Both entities display strong and diffuse nuclear TFE-3 expression.
Epithelioid inflammatory myofibroblastic sarcoma (epithelioid inflammatory myofibroblastic tumor)
It presents as large intra-abdominal mass in the mesentery or omentum with predilection for young adult males. This tumor is characterized by large anaplastic rounded or epithelioid cells with vesicular nuclei resulting in a ganglion-cell like morphology. The neoplasms harboring the *ALK-RANBP2* fusion show distinctive nuclear membrane ALK immunoreactivity. The differential diagnosis encompasses anaplastic large cell lymphoma, epithelioid leiomyosarcoma, melanoma, epithelioid rhabdomyosarcoma, dedifferentiated liposarcoma of mesentery, high-grade myxofibrosarcoma and undifferentiated carcinoma.
There are **recently described miscellaneous epithelioid** soft tissue neoplasms, such as **GLI1-Altered malignant epithelioid soft tissue neoplasms** and **CIC-NUTM1-rearranged sarcoma and related entities.**
Epithelioid variants of **myxofibrosarcoma**, **rhabdomyosarcoma**, **dedifferentiated liposarcoma** and **pleomorphic liposarcoma** have also been reported.

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Update on Myxoid Soft Tissue Tumors

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The myxoid soft tissue (S.T.) tumors are characterized by the presence of abundant loose extracellular matrix material, often rich in glycosaminoglycans. It is a heterogeneous group of lesions that can be benign, intermediate or malignant. They can often cause problems in the diagnosis because of their clinical and histologic overlapping and because of the fact that any S.T. tumor can be myxoid to some extent.

The key features for the differential diagnosis of a myxoid lesion of soft tissues are: a) the depth of lesion (superficial: dermal – subcutaneous, deep: subfascial), b) the extent of myxoid stroma (abundant – limited, diffuse – focal), c) the nuclear pleomorphism (presence – absence) and d) the presence of distinctive vasculature. Immunohistochemistry is not quite pivotal in this category of neoplasms, except for specific entities e.g. low-grade fibromyxoid sarcoma expresses MUC4. Also, cytogenetics and molecular genetics can contribute in the final diagnosis, e.g. *EWS-NR4A3 gene* rearrangement in extraskeletal myxoid chondrosarcoma.

In general, superficial myxoid tumors are benign and deep ones are often malignant. This rule has exceptions, e.g. the intramuscular myxoma is deep and myxofibrosarcoma is classically superficial. The benign myxoid lesions include the: ganglion cyst (tumor-like), intramuscular/cellular myxoma, juxtaarticular myxoma, dermal nerve sheath myxoma, superficial acral fibromyxoma (digital fibromyxoma), superficial angiomyxoma, deep ("aggressive") angiomyxoma, myoepithelioma, myxoid nerve sheath tumors (myxoid neurofibroma, reticular and myxoid S.T. perineurioma, microcystic/reticular (myxoid) schwannoma, neurothekeoma (cellular / myxoid)) and the ossifying fibromyxoid tumor (last one usually benign).

Myxoinflammatory fibroblastic sarcoma is an intermediate neoplasm, having a significant potential for local recurrence, whereas very rarely metastasizes. The malignant myxoid S.T. tumors include: myoepithelial carcinoma, ossifying fibromyxoid tumor (rarely malignant), myxofibrosarcoma, myxoid liposarcoma, extraskeletal myxoid chondrosarcoma and low-grade fibromyxoid sarcoma.

Of course, there are many other S.T. neoplasms that occasionally display prominent myxoid stroma, such as nodular fasciitis, lipoma / WD - DD liposarcoma with myxoid stroma, dermatofibrosarcoma protuberans, solitary fibrous tumor, synovial sarcoma, malignant peripheral nerve sheath tumor, embryonal rhabdomyosarcoma, fibromatosis, smooth muscle neoplasms etc. In addition, carcinomas and sarcomas can rarely show myxoid stroma. All these entities need to be considered in the differential diagnosis and the identification of histologically conventional areas can be very helpful in the final diagnosis, with the contribution of immunohistochemistry (IHC).

Among myxoid S.T. tumors there is nuclear pleomorphism in myxofibrosarcoma, myxoinflammatory fibroblastic sarcoma and myoepithelial carcinoma. The myxoid tumors that show distinctive vascular patterns include: a) deep angiomyxoma (perivascular hyalinization with smooth muscle cells spinning off of vessels), b) myxofibrosarcoma (curvilinear vessels), c) low-grade fibromyxoid sarcoma (arcades of blood vessels), and d) myxoid liposarcoma (thin-walled branching capillaries with "chicken-wire" or "crow's feet" pattern).

During the last years, there have been clarifications regarding the classification of some myxoid S.T. neoplasms. For instance, recent studies found no *GNAS gene* mutations in juxtaarticular myxoma, suggesting that it is unrelated to the intramuscular / cellular myxoma which, despite their histological similarities, it contains activating mutations in codon 201 of the *GNAS gene*. Also, cellular/myxoid neurothekeoma is now clear that has no relation to the dermal nerve sheath myxoma (formerly also referred to as *myxoid neurothekeoma*); the two lesions show differences immunohistochemically (cellular neurothekeoma: S100 protein -, SOX10-, NKI/C3+) and clinically, since dermal nerve sheath myxoma has a high rate of local recurrence, up to 45%, in contrast to the up to 10% recurrence rate of neurothekeoma.

In addition, recent studies demonstrated monoallelic deletions of the 13q12 in the superficial acral fibromyxoma (digital fibromyxoma), including the tumor suppressor *gene RB1*, resulting in loss of RB1 expression. The superficial angiomyxoma - sporadic or in the setting of Carney complex - is associated with inactivating mutations in *PRKAR1A gene*, that encodes protein kinase A regulatory subunit 1-alpha, leading to loss of PRKAR1A expression in up to two thirds of tumors. Deep angiomyxomas show nuclear expression of HMGA2 immunohistochemically; in a subset of this entity, translocations in 12q15 have been reported, resulting in rearrangement of *HMGA2 gene*. *PHF1 gene* rearrangements are characteristic and frequent in ossifying fibromyxoid tumor, found in typical, atypical and malignant variants.

Regarding myoepithelioma / myoepithelial carcinoma and mixed tumor, they are considered related neoplasms with a morphologic continuum, and myoepithelial neoplasms of S. T. are histologically analogous to those arising in the salivary glands. In children, carcinomas are more common than myoepitheliomas. Molecular genetics can identify *EWSR1 gene* rearrangements in 50% of myoepithelial tumors of skin and soft tissue (fusion partners so far: -PBX1, -ZNF444, -POU5F1, -KLF17). About 50% of fusion partners remain to be determined. Also, *FUS gene* rearrangements have been reported and *PLAG1* gene rearrangements are often seen in mixed tumors of S. T. Immunohistochemically, except for the typically used immunostains e.g. S100 protein, AE1/AE3, EMA, GFAP etc., another stain (nuclear) expressed in mixed tumors is PLAG1, similar to their salivary counterparts. INI1 loss of expression is found in a subset of myoepithelial carcinomas (10% in adults, 40% in children).

The myxoid liposarcomas most often harbor the translocation t(12;16)(q13;p11) (*DDIT3* fused with *FUS gene)*; in 10% of cases there is t(12;22)(q13;q12) translocation (*DDIT3* fused with *EWSR1 gene).* In extraskeletal myxoid chondrosarcoma the role of cytogenetics (FISH) is important, whereas immunohistochemistry has a limited value. Specifically, four balanced chromosomal translocations have been reported; t(9;22)(q22;q12) is the most common (50-70% of cases) and juxtaposes *NR4A3* and *EWSR1 gene*. The others are: t(9;17)(q22;q11), t(9;15)(q22;q21), t(3;9)(q11-q12;q22), t(9;16)(q22;p11.2), all include *NR4A3 gene*. Recently there has been reported *HSPA8-NR4A3 gene* fusion, as well as deletions or mutations of *SMARCB1 gene,* the last in a small subset of cases particularly with rhabdoid morphology.

In 95% of low grade fibromyxoid sarcomas there is t(7;16)(q34;p11) translocation (*CREB3L2 - FUS gene);* also there is t(11;16)(p11;p11) (*CREB3L1 - FUS gene)* and they may rarely harbor *EWSR1 – CREB3L1 gene fusion.* Regarding myxoinflammatory fibroblastic sarcoma, it harbors consistent t(1;10)(p22;q24) rearrangement (*TGFBR3 - MGEA5 gene),* often along with 3p11-12 amplification**.** Recent studies showed t(1;10) in hemosiderotic fibrolipomatous tumor as well, suggesting they may be morphologic variants of the same entity.

Ancillary tools (IHC – cytogenetics) can contribute to the correct diagnosis of myxoid S.T. lesions when are used after taking into consideration the clinical, imaging and pathologic features.

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The Role of the Oncologist

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Sarcomas are a heterogenous group of rare solid tumors of mesenchymal origin with distinct clinical and pathological features. They account for approximately 1% of all adult malignancies and 15% of pediatric tumors. With more than fifty subtypes of soft tissue sarcomas there are specific approaches for their treatment. The most common soft tissue sarcomas that oncologists come across in everyday clinical practice include undifferentiated pleomorphic sarcoma, GIST, liposarcoma and leiomyosarcoma. The primary treatment is influenced by the anatomic site with extremities, trunk, visceral retroperitoneum and head-neck being the most common primary sites. Metastatic disease owed to soft tissue sarcomas is usually seen in the lung whereas tumors of the abdominal cavity tend to metastasize to the liver and peritoneum. Soft tissue sarcomas are optimally managed by a multidisciplinary team of clinicians. In case of resectable disease, surgery should be the primary treatment modality along with radiotherapy and chemotherapy as deemed appropriate in each individualized case. Key determinants of systemic chemotherapy administration in patients with unresectable or metastatic disease include histology, previous therapies, performance status and the primary goal of the treatment. Doxorubicin, ifosfamide, gemcitabine, taxanes and liposomal doxorubicin are among the chemotherapy agents applied in most soft tissue sarcomas if they are chemo-sensitive, but in cases of chemotherapy resistant histology targeted agents are considered in select situations. Clinical trials are always an option for the patients where enrollment is critical in validating new therapeutic strategies for the expansion of the current armamentarium against soft tissue sarcoma.

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