

March 2016 SUP Newsletter

Message from the President



Spring greetings, microscopists,

Here's to hoping for no more "white precipitation" and that spring will be "busting out all over" soon, as is sung in the musical "Oklahoma". Below are a few notes and reminders, plus a new addition by Dr. Jan Orenstein inviting your comments and discussion.

With all best wishes for 2016.

Sara Miller

President, SUP

saram@duke.edu

Website

New website in progress

Our webmaster Charlie Register and Dr. David Howell have been hard at work to update our website because of a forced change in the way it's presented...something about "Drupal" (which sounds to me like a cross between double and triple, but I don't think that's what it means). Anyway, it has required a lot of extra work on Charlie's part, and we're eternally grateful for his dedication.

Cases of the month

We would like to revive the placement on our website of interesting cases in which electron microscope was instrumental in diagnosis. If you have potential material, please contact Dr. Howell (david.howell@duke.edu).

References

There is a publication list of ultrastructure on our website that is good but not up to date. If you know of excellent EM atlases or review articles, please send them to Dr. Howell or to me.

Dr. Josep Lloreta is editing a book on ultrastructural pathology that should be out later this year. Be on the lookout for this excellent edition.

Training courses and meetings

UltraPath 101

We are still negotiating to try to offer another training course like Dr. Gary Mireau's excellent UltraPath 101 this past September. We will keep you posted on that. For now, do note that a similar program will be offered by Dr. Josep Lloreta just prior to our biennial meeting in Lisbon. I hope that many of you will be able to take advantage of that.

SUP at USCAP 2016

Our program this year on *Small Blue Cell Tumors has been organized by Dr. Guillermo Herrera*. It will be held Sunday, March 13, 2016, from 8:30 AM - 12:00 PM in room CC 605. Topics are listed below.

Moderator: Guillermo A. Herrera, MD, *LSU Health, Shreveport, LA*

Course Description:

The topic of this year's meeting was determined by the Society for Ultrastructural Pathology Board of Directors. Open deliberation of its members concluded this was a timely topic to address at the USCAP. It was chosen as this group of tumors often requires the use of various techniques for their speciation. The value of the use of ancillary diagnostic techniques, including electron microscopy, in the diagnosis of this group of neoplasms is well recognized. Ultrastructural pathology plays a key role in the diagnosis of small blue cell tumors. The target audience includes: general surgical pathologists, trainees, academic pathologists, and ultrastructural pathologists and technicians/scientists who engage in diagnostic transmission electron microscopy.

8:30 AM	Small Blue Cell Tumors in the Lung Victor Roggli, MD (presented by Elizabeth Pavlisko, MD), <i>Duke University Medical Center, Durham, NC</i>
9:15 AM	Small Blue Cell Tumors in Children John Hicks, MD, PhD, <i>Texas Children's Hospital, Houston, TX</i>
10:00 AM	Break
10:30 AM	Cytology of Small Blue Cell Tumors Elba A. Turbat-Herrera, MD, <i>LSU Health, Shreveport, LA</i>
11:15 AM	Small Blue Cell Tumors in Soft Tissue and Bone Cyril Fisher, MD, DSc, FRCPath, <i>Sarcoma Unit, Royal Marsden Hospital, London, England</i>

UltraPath XVIII in Lisbon

As a reminder, UltraPath XVIII will be held July 11-15, 2016, and information is on the conference web site at <http://congress.ultrath18.org> . Please register online and note that the deadline for abstracts is coming up soon on March 23, 2016. A note from the meeting chair is below.

Dear Colleagues,

The Organizing Committee of Ultrath XVIII has extended the deadline for abstract submission to March 23, 2016. The programme of the Congress is advancing fast and participants' contributions are being received following the interest raised among the Ultrastructural Pathology community worldwide. Check out some of the invited speakers on the Congress web site (<http://congress.ultrathxviii.org>).

For the memorial session to Feroze N. Ghadially we will be honored to have the participation of Dr. Ghadially's daughter, Dr. Ruby Ghadially. Please contribute with your knowledge and experience to this unique Congress by submitting your abstract and sharing your work with your colleagues.

With kind regards from the Organizing Committee,

A.P. Alves de Matos
Chair of Ultrapath XVIII

UltraPath XIX

Dr. Giovanna Crisi is working on finding a location for the UltraPath meeting after Lisbon and is considering the north-eastern part of the USA. If you have suggestions or would like to assist, please contact Giovanna (Giovanna.Crisi@baystatehealth.org).

New newsletter addition

Jan Orenstein, MD, PhD, a long time member of the society, has now retired from the practice of pathology and is engrossed in sorting his gazillions of micrographs and writing papers. He has expertise in infectious diseases, among other things such as unusual ultrastructure. Jan has volunteered to write a series of short articles that reflect several decades of his study and observation. These will appear in our upcoming newsletters, and as you know, the newsletters can be found on our website. He asks that members use this as a vehicle for a discussion and that you email him your comments and questions (jmo@gwu.edu). Please also copy me, and I will add them to the next newsletter (saram@duke.edu).

Orenstein Newsletter Nugget #1

Ultrastructure is the gold standard of morphology and a key to cell biology!

Jan Marc Orenstein, MD, PhD

Dedicated to Dr. Feroze Ghadially, our mentor!

Historically ultrastructure has been the gold standard for cell/tissue morphology, biology, biochemistry, diagnostic pathology, and should play an important role in personalized medicine. TEM can play a critical role in the verification of the diagnosis, such as in tumor identification.

Also, it can be a means by which to validate isolated/purified cells that will be employed in biochemical and molecular studies. Omission of TEM likely makes the studies suboptimal and wasteful. It is obvious that we must get involved in clinical studies, either as in individuals in a single institution or as a collaborating group; the greater the numbers the greater the statistical validity and impression. We must convince study directors of the power and advantage of adding TEM evaluation.

Unfortunately, diagnostic pathology is increasingly under pressure to determine "what is this" in deference to "why it is this way"; pathologists are the scientists of modern medicine. Whether in surgical or autopsy pathology, pathologists are not too late; they are the windows of the future. We are uniquely privileged to have access to clinical specimens and autopsy tissues; thus, we should make every effort to view all specimens as potential opportunities to learn, to consider something that one takes as simply routine or even boring. Otherwise, one could be missing something potentially important. Even autopsy tissue from paraffin blocks may be informative.

In over 40 years of diagnostic and eclectic research pathology, I have never discarded an electron micrograph (8"x10" print) taken in my laboratory, the result of which has been being able to find new ways of seeing things and finding the answers to new questions. For example, the ~50 year-old fibroblast/myofibroblast issue was relatively easily resolved when it was clear from my material and the literature that fibroblasts have always had stress fibrils, and there

there was never a need to invent the “myofibroblast”; in reality, myofibroblasts are actually morphologically and functionally exactly the same as fibroblasts. Because there is no specific marker for the fibroblast and LM is difficult at best, TEM was the best method for identification. However in trying to make it easier, researchers replaced TEM with smooth muscle actin (SMA) immunohistochemistry of short filamentous actin (SF actin), and in doing so, forgot that there are other important cells in many lesions that have SF actin and, likewise, stain by IHC (e.g., pericytes, EMCs, pericytes, and endothelial cells). Thus, the diagnosis of soft tissue tumors has been undermined.

An ultrastructuralist is also privileged to be able to help provide information that is increasingly considered critical in the stroma of carcinomas, which includes the field of carcinoma-associated fibroblasts (CAFs). Up to now, a CAF has been considered to be a myofibroblast, a cell that the never was, instead of the fibroblast that has always been. This is based on the erroneous SMA stain. Primary and metastatic cancers stimulate their fibroblastic stroma *de novo*, and they, apparently, are in constant communication (symbiosis). This whole area requires TEM study. I have already distinguished two morphologically distinct stromal fibroblasts in different areas of carcinomas. One in particular is a bit baffling, since it also is found in the same relationship to normal structures in the body, although not in the same abundance and not as pleomorphic. I need your help here. A good rule is always to preserve stromal areas of all tumors; the diagnosis comes first, but there is so much more

to observe.

While IHC is a helpful tool, we must realize that it is not only limited by its sensitivity and reproducibility. In reality, you can't prove a marker is not present in a specimen; it is just that you haven't detected it.

I would like to give my first set of observations that were revealed from scrutinizing my electron micrograph repository and might be of interest to you. I would appreciate feedback so that we can all learn from each other: there will be room for your comments in our next Newsletter.

1. As with their rough endoplasmic reticulum (RER) organelles, fibroblasts have always had peripheral stress fibril contractile organelles; it is just that their dense bodies [as in smooth muscle cells (SMC)] were not visualized until 1960. Therefore, the invention of the "myofibroblast" was unnecessary, and the smooth muscle actin (SMA) of the stress fibril actin was considered a blessing and an easy way out; in fact it created mistakes. It is difficult to fathom that for nearly 50 years we have been living with a cell that never was. What is your opinion?

2. Since the basal lamina (Are we the only ones who know the difference between the basal lamina and the basement membrane?), is synthesized by carcinoma cells, as are the terminal bar/apical junctions, the idea that "breaching the basal lamina" by carcinoma cells as they invade the stroma doesn't make sense; i.e., it is not a barrier; it is a product of the cell. Comments?

3. Luse bodies are formed mysteriously from the external layer almost exclusively of Schwann cells (They can be quite subtle, but are always esthetically pleasing.), while the long-spaced collagen (LSC) is an aberrant form of banded collagen caused by the swelling of dissociated Luse bodies. Inexplicably, LSC is a very common feature of the stroma of sclerosing Hodgkin's disease, and interestingly, when banded collagen is allowed to dissociate *in vitro* and then allowed to repolymerize, you get LSC. Comments?

4. Is the diagnostic significance of the rhabdoid vimentin structure only a pathologically significant form of a renal tumor, since such structures are seen in carcinomas and even sarcomas? In those cases, some may also be composed of actin or cytokeratin: does that make a difference? How does one explain clinically the frequent TEM overlapping of the three types of renal tumor morphologies (common lipid/glycogen, oncocytic, and chromophobe)? It must mean something clinically; LM can't always appreciate the structure, as TEM does.

5. There must be more that separates amelanotic melanomas from typical melanomas than simply the appearance of the melanocytes, e.g., origin, behavior, prognosis, or stroma. What could it be?

6. Why do squamous carcinoma cells have some stress fibrils?

7. Is there really such a lung tumor as an "adenosquamous carcinoma"? Do all adenocarcinomas have cytokeratin? By the way, squamous cells are the only normal epithelial cells that have cytokeratin; the cytokeratin in tumors is synthesized *de novo*.

It is time to go with the flow of so-called personalized medicine; we have so much that is unique to contribute, and now we have to prove it. Please contact me at jmo@gwu.edu , or send comments to Sara for the newsletter at saram@duke.edu to start a discussion.

