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FOCUS

PAPANICOLAOU SOCIETY OF CYTOPATHOLOGY

Companion Society of the United States and Canadian Academy of Pathology

Dedicated to Clinical Practice, Clinical Education and Clinical Research

From the Editor's Desk

Dear colleagues,

It is time for yet another issue of Focus!

Readers will have timely topics on cell block variation in the era of molecular diagnostics and personalized medicine. The section on images in Cytology should lighten the mood.

The president's message reflects the change in PSC leadership. Please join me in welcoming Dr. Tarik Elsheikh starting his presidency after USCAP 2015 at Boston.

PSC members enjoy variety of benefits including total waiver of $ 1500 article publication charges for accepted CytoJournal manuscripts during membership as OA Stewards- plus status of PSC with Cytopathology Foundation. This and other benefits are highlighted on the last page. Please spread the word and recommend your colleagues to join PSC by sending the membership form downloaded from http://www.papsociety.org/docs/09/pscapp2009.pdf

Please submit the articles or other contributions (eg. interesting images in cytology, book reviews, case reports, reviews etc) to future Focus issue by sending those to me or any of the Focus editorial board members.

Currently we are accepting submissions for the June 2015 edition. The deadline for submitting the contributions are flexible, but we appreciate if your submissions are received at vshidham@med.wayne.edu prior to May 1, 2015.

Happy reading!

Sincerely,

Vinod B. Shidham, MD, FRCPath, FIAC

President's Message

Zubair W. Baloch, MD, PhD

Preserving the Legacy of Cytopathology

"Maybe you are searching among the branches, for what only appears in the roots."
- Rumi

As the moment draws close to me being the "Immediate Past President" of Papanicolaou Society of Cytopathology (PSC); I am focused, now more than ever before, on preserving the basic educational concepts and the legacy of cytopathology. I feel this more than usual when we are faced with shrinking numbers of cytotechnology schools, greater promise to our clinical colleagues of richly advertised techniques which may replace the need for cytomorphology and lack of trained cytopathlogy professionals in underdeveloped countries. On occasion, I do consider myself a "Seasoned Pathologist"; and pose a question to myself "Are we Training enough cytopathology professionals"?

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In This Issue

Membership Application

(Please download, print and complete)
http://www.papsociety.org/docs/09/pscapp2009.pdf

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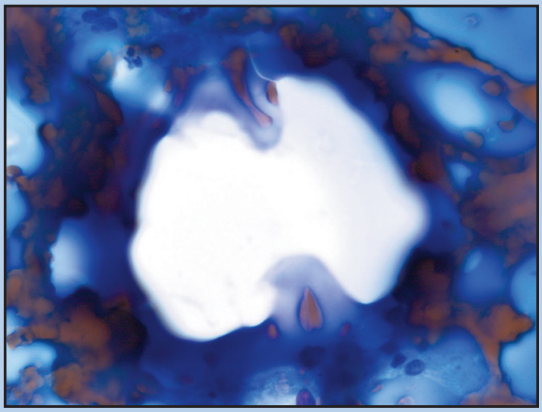
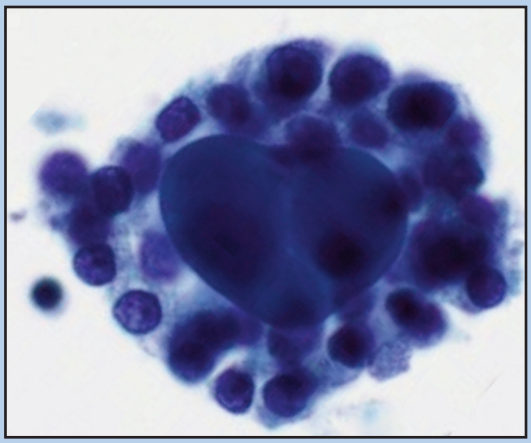
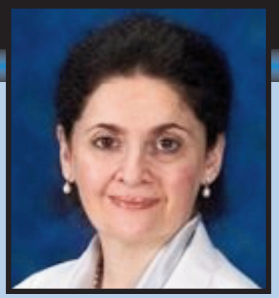
Images in Cytology







The Art and Heart of Thyroid Fine Needle Aspirations

Colloid in fine needle aspiration specimens of the thyroid gland may have different appearances, depending on the type of preparation, staining, and even the nature of the aspirated lesion. Colloid can be thin or watery, thick or chunky. It has been described as cracked, with "geographic" pattern, two-tone, spider-web-like, bubble gum, chicken-wire or Swiss-cheese-like, etc. In these two air-dried Diff-Quik-stained smears from benign follicular nodules abundant colloid material created an artistic appearance of the butterfly-like organ that produced it, and took a shape of heart within the follicle that synthesized it.

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Con't from page 1

From the President's Desk

And is the teaching of basic techniques and morphologic concepts such as "making a good smear" are taking the back seat in view of lustrous techniques and tests in our field?

To this day I very much enjoy listening to my idols in cytopathology, who so eloquently teach the building blocks of cytopathology. To name few of my favorites; Dr. Prabodh K. Gupta spending hours illustrating "why a cell is malignant" or Dr. Britt-Marie Ljung stressing in national meeting the importance of a well-fixed cytologic preparation for rendering cytologic diagnosis. I am holding on to these teachings; but I am also afraid that in the future they may only exist in the dusty pages of large textbooks or less stressed upon in view of ever growing demands on our profession; so called "keeping up with times". I do whole heartedly recognize the efforts of our professional societies who continue to deliver balanced and wholesome cytopathology education which equally stresses morphology well as the new developments. However, it is also very crucial that we recognize our individual responsibility in continuously seeking harmony in our field; before we are named only the "facilitators" not the "renderers" of the cytologic diagnosis.

Dr. Tarik Elsheikh will be starting his presidency of PSC after this year's USCAP meeting in Boston. I have known Tarik for many years as a friend and an educator; his resume illustrates many professional and educational achievements. I believe his biggest undertaking so far was organizing a successful basic cytomorphology course at annual meeting of United States and Canadian Academy of Pathology. This course was initially advertised for trainees in pathology and cytopathology, however, to my surprise even practicing pathologist found it very helpful for reinforcing concepts in basic and organ based cytopathology. This is a testament of preserving and strengthening the foundations of our profession. I am certain with the help of its members and officers, Tarik will continue to promote PSC as a society which collaborates with other societies to sustain "The Legacy" of cytopathology in face of new developments and challenges.

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Research Article

The state of cell block variation and satisfaction in the era of molecular diagnostics and personalized medicine

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Abstract

Background: In the recent past, algorithms and recommendations to standardize the morphological, immunohistochemical and molecular classification of lung cancers on cytology specimens have been proposed, and several organizations have recommended cell blocks (CBs) as the preferred modality for molecular testing. Based on the literature, there are several different techniques available for CB preparation-suggesting that there is no standard. The aim of this study was to conduct a survey of CB preparation techniques utilized in various practice settings and analyze current issues, if any. **Materials and Methods:** A single E-mail with a link to an electronic survey was distributed to members of the American Society of Cytopathology and other pathologists. Questions pertaining to the participants' practice setting and CBs-volume, method, quality and satisfaction-were included. **Results:** Of 95 respondents, 90/95 (94%) completed the survey and comprise the study group. Most participants practice in a community hospital/private practice (44%) or academic center (41%). On average, 14 CBs (range 0-50; median 10) are prepared by a laboratory daily. Over 10 methods are utilized: Plasma thrombin (33%), HistoGel (27%), Cellient automated cell block system (8%) and others (31%) respectively. Forty of 90 (44%) respondents are either unsatisfied or sometimes satisfied with their CB quality, with low-cellular yield being the leading cause of dissatisfaction. There was no statistical significance between the three most common CB preparation methods and satisfaction with quality. **Discussion:** Many are dissatisfied with their current method of CB preparation, and there is no consistent method to prepare CBs. In today's era of personalized medicine with an increasing array of molecular tests being applied to cytological specimens, there is a need for a standardized protocol for CB optimization to enhance cellularity.

Key words: Cell block, cytopathology, fine-needle aspiration, lung cancer, molecular testing, personalized medicine

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INTRODUCTION

Classically, cytomorphologic diagnoses have been rendered on Diff-Quik and Papanicolaou-stained smears. Other techniques have been introduced to this traditional method, including cytospins following specimen concentration, thin layer preparations with selective cellular enhancement and cell blocks (CBs) from sample consolidation. Each modality and stain offers its advantages.

Though other preparations may impart greater cytomorphological detail, CBs are recognized for their semblance to histology, including potential to identify architectural features similar to those observed in histological sections,[1,2] especially in the presence of tissue fragments. Furthermore, CBs have the capacity to yield multiple tissue sections for ancillary tests, including special stains, immunohistochemical (IHC) stains with co-ordination of immunoreactivity pattern and molecular diagnostics. Recent expert consensus opinion on molecular guidelines for selection of lung cancer patients for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors issued by the College of American Pathologists, International Association for the Study of Lung Cancer and Association for Molecular Pathology states that CBs are preferred over smear preparations for polymerase chain reaction-based EGFR testing and fluorescence *in situ* hybridization assay for ALK.[3] For these reasons, CBs, which have served as adjuncts to the conventional approaches for diagnosis, are now considered an integral component of the repertoire of cytology preparations, particularly for lung cancer specimens.[3,4]

Several advances in other aspects of medicine have heightened clinical awareness and utility of CBs.[5] There is a strong trend toward the clinical use of minimally-invasive procedures. Not only are they less invasive than surgical alternatives, but they can be performed on an outpatient basis with fewer resources. For patients with (suspected) lung cancer in particular, endobronchial ultrasound-guided fine-needle aspirations (FNAs) have the capacity to provide diagnostic and staging information at the same time.[6] With the capabilities of minimally-invasive procedures and a concurrent emphasis on personalized medicine and molecular diagnostics, the provided specimen size has decreased while the information required from the sample has increased. Because greater numbers of ancillary tests are routinely requested and CBs, comprised of fewer cells than their histological resection counterparts, may represent the only diagnostic tissue ever attained from a patient, a greater burden has been placed on pathologists.[7] Fortunately, progress in molecular techniques enables the use of less tissue, including cytological samples.[8] In fact, ancillary tests results paralleling those reported on histological resections have been reported on CBs; the outcomes are not uniform across studies, however. Though there are several possible contributing factors to the variations, the aim of the current study was to focus on CB-related issues.

MATERIALS AND METHODS

Institutional Review Board approval was not obtained for this research, since it did not require review of any patient information. A link to an electronic survey was distributed through electronic mail (e-mail) to members of the American Society of Cytopathology and other pathologists. Only a single e-mail and no repeat reminder E-mails or incentives, were sent. Questions included in the survey are listed in Figure 1. All questions, except one, were in a multiple-choice format, with 2-8 responses for each. Respondents were permitted to choose only one answer for some and >1 for the remaining. Furthermore, provided was an "Other" option with free text capability for some questions. The one question without multiple choices had a slider with a value scale ranging from 0 to 50. All responses were tabulated and replies to the "Other" options were recorded.

Statistical analysis was calculated on Excel using *t*-statistic two-tailed test and *P* values were calculated using 0.05 significance.

RESULTS

Of 95 respondents, 90 (95%) completed the survey and comprise the basis of this study. Most participants work in a community hospital/private practice (44%) or an academic center (41%); 7% work at a commercial laboratory and the remaining at an independent lab, military facility, or VA Medical Center.

Eighty-nine (99%) of respondents examine cytology specimens and consider CBs to be an integral part of cytological specimens. On average, 14 CBs (range 0-50; median 10) are prepared by a laboratory daily. Many participants (n = 40; 44%) are either unsatisfied or sometimes satisfied with the quality of CBs prepared in their laboratories, with low-cellular yield being the leading cause of dissatisfaction (33%) [Figure 2].

Over 10 different methods are utilized to make CBs and include plasma thrombin (33%), HistoGel (27%) (Thermo Scientific Richard-Allan Scientific; Kalamazoo, MI, USA), the Cellient automated cell block system (CACBS) (8%) (Hologic) and other methods (31%); only one (1%) respondent did not make CBs and some used >1 method [Table 1]. HistoGel and plasma thrombin were used almost equivalently at academic centers and in community hospitals/private practices [Figure 3].

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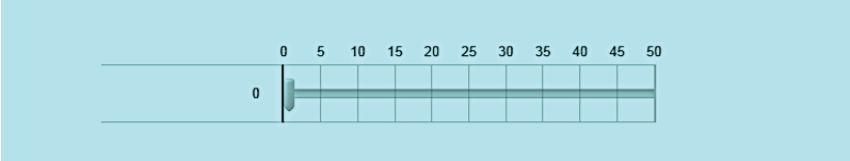
1. Which of the following best des cribes your work establishment?

- ○ Academic center
- ○ Commercial laboratory
- ○ Community hospit al/ private practice
- ○ Other [ ]

2. Do you examine cytology specimens?

- ○ Yes
- ○ No

3. Approximately how many cell blocks does your laboratory process in a single day? Please slide the bar horizontally to the right.



4. Do you believe that cell blocks are an integral part of cytology specimens, such as fine needle aspirates?

- ○ Yes
- ○ No

5. **Which of the following methods is used most frequently to prepare cell blocks in your laboratory? Please select all that apply.**

- ☐ Cellient
- ☐ Histogel
- ☐ Plasma thrombin
- ☐ Other [ ]
- ☐ We do not make cell blocks.

6. Are you satisfied with the quality of cell blocks prepared in your laboratory?

- ○ Yes
- ○ No
- ○ Sometimes
- ○ Not applicable

Figure 1: Contd...

7. If you are unsatisfied with the quality of cell blocks, which of the following are the main contributing factors? Please select all that apply.

- ☐ Often unsatisfactory (low cellular yield)
- ☐ Samples are too small to process
- ☐ Time consuming
- ☐ Labor intensive; not enough laboratory personnel
- ☐ Risk of cross contamination
- ☐ Other
- ☐ Not applicable.

8. If your laboratory USES the Cellient system to process cell blocks, which of the following was/were the driving reason(s) for its purchase? Please select all that apply.

- ☐ Automation
- ☐ High cellular yield
- ☐ Decreased contamination risk
- ☐ Rapid processing time
- ☐ Ability to process small biopsy specimens
- ☐ We do not use Cellient.
- ☐ Other

9. If your laboratory DOES NOT USE the Cellient system to process cell blocks, which of the following is/are reason(s) for not adopting it? Please select all that apply.

- ☐ Cost
- ☐ Inability to use formalin
- ☐ Unsure if immunostains are valid on Cellient-prepared cell blocks
- ☐ Unsure if molecular tests are valid on Cellient-prepared cell blocks
- ☐ Only a single block can be processed at a time
- ☐ Unfamiliar with Cellient system
- ☐ We use Cellient.
- ☐ Other

Figure 1: Survey questions

Among the three most common methodologies (plasma thrombin, HistoGel and CACBS) analysis of satisfaction of CB quality (differences in the proportion of "Yes" [satisfied] and "No/Sometimes" [unsatisfied/sometimes satisfied] responses) demonstrates that HistoGel scores the lowest, but the results are not statistically significant ($P = 0.09$) [Figure 4].

The main driving factors for utilization of CACBS by the eight participants include enhanced cellular yield, rapid processing time and ability to process small biopsies [Figure 5]. High cost is the main reason for not employing CACBS [Figure 6].

Table 1: Methods most commonly used to prepare cell blocks

Plasma-thrombin: 33%*	***Histogel: 27%****	***Cellient: 8%****
CytoRich red pellets	Sedimentation	Penfix/formalin
Formalin/alcohol mix or agar	EtOH/ concentration/filter	5% alcoholic formalin
Zinc formalin or agar	Formalin	Naturally forming clots
Pick out large fragments	Manual centrifuge and fix	Colloidin bag
2% agar	Centrifuge and place in 10% formalin	Albumin

*Numbers and percentages for the 3 most common methods. The remaining methods in this table equal 28 (33%). One participant's laboratory does not make cell blocks (1%)

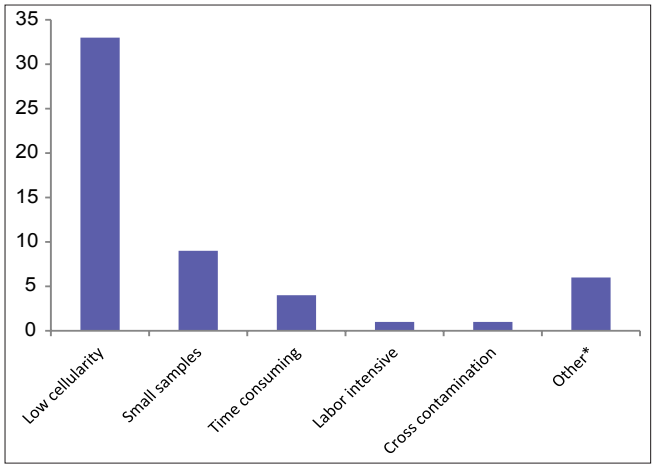


Figure 2: Main contributing factors for being unsatisfied with the quality of cell blocks (*Other: Variable cellularity/variable technicians, inter-operator variability, issues with clotting/low cellularity, poor morphology/antigenicity loss)

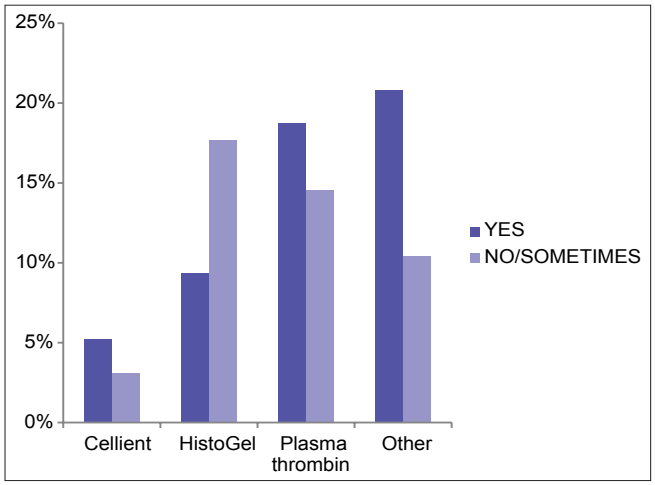


Figure 4: Satisfaction with the quality of cell blocks prepared via different methods

DISCUSSION

Morphological diagnosis is no longer sufficient.[2,4] Now, more than ever, with the identification of novel predictive and prognostic markers, management is dictated by a combination of morphological and ancillary test results,[2] especially for patients with lung carcinomas. These are not just used to make therapeutic choices, but also represent the current standards of care.[1,3,9] These changes have coincided with the performance of increasing numbers of minimally-invasive procedures, such as ultrasound-guided, computed tomographic-guided and navigational bronchoscopic-guided FNAs[4] for sampling lung, pancreas, other gastrointestinal lesions and/or lymph nodes. For patients with locally advanced and/or metastatic cancer,[2] cytology specimens, such

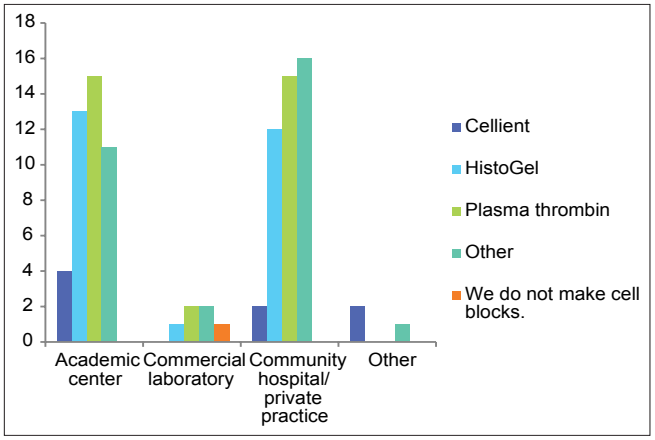


Figure 3: Most frequently used methods to prepare cell blocks in different types of work establishments

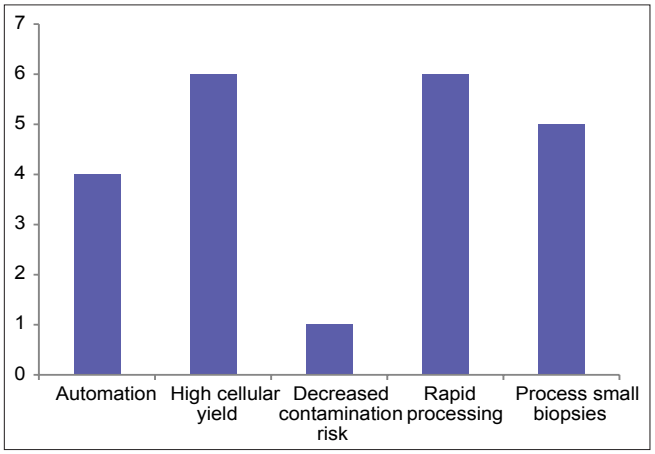


Figure 5: For laboratories using the Cellient system, this graph shows the driving reasons for purchasing the system to prepare cell blocks

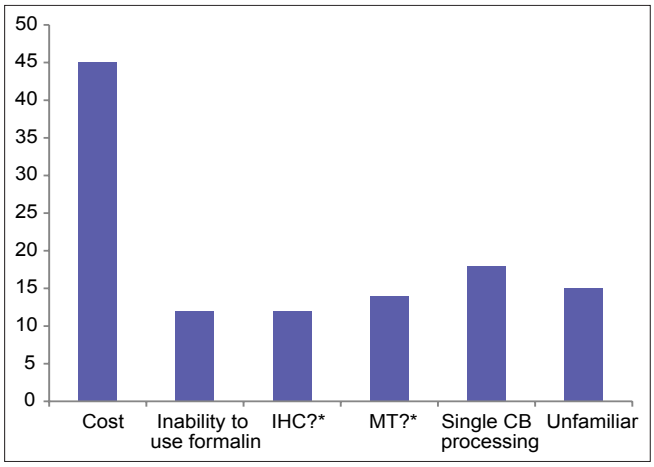


Figure 6: For laboratories not using the Cellient system, this graph shows the driving reasons for not adopting the system to prepare cell blocks (*IHC = Immunohistochemical stains; MT = Molecular testing. Question marks = Unsure if immunohistochemical stains and molecular tests are valid on Cellient-prepared cell blocks)

as pleural fluids, peritoneal fluids or FNAs,[3] may provide the only source of diagnostic tissue upon which therapeutic decisions are rendered[1] and selection for clinical trials is determined.[2] This has culminated in greater expectations from pathologists, particularly those practicing cytopathology, to perform an increasing array of ancillary tests-IHC and molecular tests-on smaller cytology specimens and provide satisfactory results to guide therapeutic decisions.[4,10,11]

In the past, there have been no standardized guidelines dictating the type of cytology specimen that should be utilized for such ancillary testing. Moreover, there are studies describing EGFR testing on various cytological preparations. This provides a range of options but also limits standardization.[12] Current expert consensus opinion,[3,11,13] including by the International Association for the Study of Lung Cancer, American Thoracic Society, European Respiratory Society and College of American Pathologists,[3,14] however, advocates CBs over direct smears to carry out these analyses.[3,14]

Usually >1 different preparations, including smears, cytospins, liquid-based preparations and/or CBs are routinely used for cytomorphological diagnosis. CBs, first introduced in the late 1960s and early 1970s,[15,16] offer several advantages, including architectural organization correlating to histology and recognition of intercellular bridges of squamous cell carcinomas not readily seen on other cytological preparations.[1] Also, by being able to view the morphology, the cells of interest can be correlated from level to level and the tumor content of the specimen can be assessed, specifically the tumor volume and percentage,[3,4] in order to determine if the sample is adequate for molecular testing (MT). Residual material from the ThinPrep vial offers an alternative, but determining the ratio of tumor to total cellularity may be difficult and has potential to lead to interpretive errors when the ratio is low. In addition, CBs serve as a source of additional material,[3] so that diagnostic preparations (e.g., smears) do not have to be compromised for ancillary testing, which can have possible downstream medicolegal implications.

Like formalin-fixed histology paraffin blocks, CBs allow for long-term specimen preservation and supply archival deoxyribonucleic acid (DNA) for future diagnostic studies[3,9] and research. CB sections furthermore provide the opportunity to have material that is fixed in 10% neutral-buffered formalin, on which a majority of molecular assays have been optimized and validated on surgical pathology specimens.[3] Finally, because they can be processed like paraffin-embedded sections, CBs easily integrate into existing methods for histochemical, IHC and MT[3,4] and the results are similar to those obtained on paraffin-embedded tissue sections.[17] Despite the numerous advantages of CBs, the cellular yield of CBs is inconsistent and varies widely.[18-20]

Given the recent emphasis, the aim of the current study was to focus on the current status of CBs. The survey was completed by 90 pathologists and cytotechnologists from various work settings, ranging from academic centers and commercial laboratories to private practices and thus provides a representative cross-section. Based on the survey, 95% (90/95) of respondents practice cytology and consider CBs to be an integral part of cytological specimens; one respondent who works in a commercial laboratory did not process CBs. The different CB preparations are used comparably in academic centers, community hospitals and private practices [Figure 3]. On average, 14 CBs (range 0-50; median 10) are prepared by a laboratory daily. Currently laboratories use a variety (>10) of methods to prepare CBs [Table 1]. These techniques, each with its unique traits, protocol and advantages, have been described.[2,18,21-24]

Many survey participants (n = 40; 44%) are either unsatisfied or sometimes satisfied with the quality of CBs prepared in their laboratories, with low-cellular yield being a leading cause of dissatisfaction (33%) [Figure 2]. Review of the literature shows similar variability in the results of adequacy of CBs,[2] including for histologic typing and ancillary tests.[7,9,25,26]

Comparison of CB techniques

Comparison of the three most common techniques (plasma thrombin, HistoGel and CACBS) shows that HistoGel has the lowest rate of satisfaction, but the results are not statistically significant (P = 0.09). Similar results have been cited by others.[27-29] Benkovich *et al.* in their study have reported that plasma thrombin CBs were more cellular and

had better cellularity, morphology, cell distribution and pellet size relative to those prepared with HistoGel.[27,28] A second study also demonstrated that cellularity for plasma thrombin CBs was greater than for HistoGel CBs, but the latter had better cellular preservation and architecture.[28] The plasma thrombin technique also yielded better cellularity, cell distribution and background quality relative to other methods, including inverted filter sedimentation,[30] albumin method and simple sedimentation.

"Other" techniques may potentially provide greater satisfaction. An alternative solution that outperformed plasma thrombin and HistoGel is the collodion bag technique which has been suggested as a high cellular yield method.[28,31-33] The so-called tissue coagulum clot method has been shown to significantly increase the efficiency and cellular yield when compared with conventional saline rinse.[2]

Only a minority of respondents utilized CACBS in our survey; 5 were satisfied and 3 were not entirely satisfied. Though the sample size is small, there is no statistical significance (P = 0.11) between CACBS and the other non-automated "traditional" methods. A similar observation was reported, when comparing CBs prepared with CACBS and "traditional" (non-automated) methods.[33]

Interestingly, the data show that 17% respondents are unfamiliar with CACBS [Figure 6]. Those who are familiar with CACBS use it for both cytology and small biopsy specimens. For CBs, high cellular yield and decreased risk of contamination were the two most cited reasons for using CACBS; high cost was the leading reason for not using it. Other reasons for not using CACBS included an inability to use formalin and uncertainty about results of immunohistochemistry and MT. In a study comparing traditional CBs to CACBS, the majority of IHC stains showed identical results with the two methods, although there were a limited number of overall cases (17 patients; 56 IHC stains).[33]

Specimen fixation

Though IHC stains and MT may be performed on samples fixed in alcohol, most pathology laboratories have standardized immunohistochemistry protocols for formalin-fixed material.[33] When MT[3] or immunohistochemistry is performed on alcohol-fixed specimens, the laboratory needs to conduct appropriate validation studies so as to avoid false negative or false positive results. In addition, proper duration of fixation is required to obtain reliable IHC stain results. For example, at least 6-8 hours of formalin-fixation time for breast biopsies is required to obtain reliable estrogen receptor determination by immunohistochemistry;[34] inadequate fixation may lead to false negative results.[34]

Increasing cellular yield of CBs

While one or more factors may lead to suboptimal results,[6] including operators' skills,[6] inadequate lesional tissue acquisition, nature and location of the lesion,[2] inappropriate triage of the sample and lack of technical expertise in processing small specimens, the current study demonstrates that variability in CB processing techniques is likely a contributing factor. For instance, five different methods to process CBs using HistoGel were outlined by one group.[27] The literature also highlights variations in fixation,[21,26] concentration and congealing techniques.[13] Several modifications have been described. For instance, concentration of diagnostic cellular material along the cutting surface, with provision to control the depth of cutting by the histotechnologist, has been reported to yield results in 133 out of 134 liquid based cytology specimens of cervical cytology. Similar results are expected with this method using any specimen with low cellularity with loosely cohesive or singly scattered cells such as serous effusions and FNA needle rinses in saline or Roswell Park Memorial Institute (RPMI) culture medium (fresh unfixed cells) or needle rinses directly in 10% formalin.[31,32] Also, a focus on the specimen collection may play a role. Several CB preparation methods, including adding thrombin, plasma, agar gel and use of commercial assay kits, are designed primarily to concentrate cellular material after it is collected from aspiration needles. There has been interest, as with the tissue coagulum method,[2] to protect such material from loss before the preparative procedure.[2,23,35,36]

Though CBs, including FNA-derived CBs, have proven to be valid,[4] low cellular yield leads to suboptimal efficiency of CBs,[2] especially for MT. Such testing requires high tumor content (10-100 ng of DNA without necrosis) and percentage of tumor cells (>40% tumor cells).[4] Even though these can be enhanced by microdissection and the thresholds of minimum tumor content may decrease as the field of MT evolves, with scant cellularity, CBs are still likely to have low yield.

Dedicated current procedural terminology (CPT) code for processing CBs

CB preparation requires significantly greater efforts and more resources with special laboratory setup than simple grossing steps involved for routine biopsy specimens. Nevertheless, the current technical component of the CPT code for CBs is 88305, which is the same as for routine biopsies. Investment in generation of high quality and cellular CBs with incentive to use the best resources would be facilitated by introducing a special CPT code with higher remuneration for the investment. Increasing demand for better quality CBs demands expedited efforts to introduce a dedicated CPT code for its processing.

CONCLUSIONS

Accurate histological classification and MT on small samples are becoming the norm. The clinical demand for ancillary tests to guide targeted therapies is likely to grow, which means that the numbers of tests requested on cytology specimens is likely to increase also.[4] CBs provide an important medium to conduct these tests, but their cellular yield needs to be improved. Though the survey has a limited number of respondents, it demonstrates that even within a small sample, there is no consistent method to prepare CBs, and many pathologists and cytotechnologists are dissatisfied with their current method (s) of CB preparation.

The results stress the need for a better methodical approach for optimization of CBs to enhance cellularity in today's era of personalized medicine.[2,32,37] This study serves as a baseline to launch further investigation of the pros and cons of different CB preparation techniques, as comparative literature in this topic is limited. Additional studies with an in depth analysis to determine the appropriate method(s) is necessary.

Determining and standardizing the most effective technique may alleviate the variability and provide consistency. As it adapted to the introduction of immunohistochemistry and flow cytometry, cytology has to align itself with the multitude of molecular diagnostic tests.[4]

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AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article. JPC analyzed the data and drafted the study. JJH interpreted the data and revised it for intellectual content. SM and AN contributed to the design of the study and revised it for intellectual content. AS conceived the study, interpreted the data and drafted the content. All authors read and approved the final manuscript. Each author acknowledges that this final version was read and approved.

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The authors followed the ethics statement requirement(s).

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The state of cell block variation and satisfaction in the era of molecular diagnostics and personalized medicine

John P. Crapanzano, *MD*, Jonas J. Heymann, *MD*, Sara Monaco, *MD1*, Aziza Nassar, *MD2*, Anjali Saqi, *MD, MBA**

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Research Article

Frequency and characterization of celiac ganglia diagnosed on fine-needle aspiration

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Abstract

Introduction: Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) is frequently used to sample intra-abdominal lesions and lymph nodes. Celiac ganglia normally located near the celiac artery may be sampled during these procedures. The aim of this study was to determine the frequency of detection and cytologic findings of celiac ganglia diagnosed on FNA. **Materials and Methods:** A 14-year retrospective review of radiologic and endoscopic FNA cases involving the celiac region was performed. Cases in which ganglia were reported were further analyzed and slides reviewed. **Results:** A total of 354 patients underwent FNA of a suspected celiac lymph node (334 patients) or celiac mass (20 cases). In 9 of these patients (2.5%), ganglion cells were identified. These were identified in cases only after 2008 via EUS-guided FNA. Aspirates were hypocellular and bloody. Large ganglion cells were either sparsely dispersed or present in clusters. Ganglion cells had a low N: C ratio, granular cytoplasm with neuromelanin, and eccentric small round nucleus with a prominent nucleolus. One specimen had concomitant pancreatic adenocarcinoma. None of these cases had a false positive on-site adequacy assessment or final misdiagnosis. **Conclusions:** These data show that celiac ganglia may be infrequently encountered, especially with intra-abdominal EUS-guided FNA targeting nodes or masses near the celiac region. Therefore, cytologists should be aware of the possibility of finding ganglionic cells in EUS-guided FNA samples.

Key words: Celiac, cytology, endoscopic ultrasound, fine-needle aspiration, ganglion

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INTRODUCTION

The celiac ganglia innervate several intra-abdominal viscera.[1] They are located at the origin of the celiac artery, anterolateral to the aorta. There may be one to five ganglia per individual, with reported sizes ranging from 0.5 to 4.5 cm.[2] The celiac lymph nodes, located in close proximity to the celiac ganglia, are routinely evaluated during the

work up for malignancy. These nodes may be biopsied using percutaneous computerized tomography (CT) or intra-abdominal endoscopic ultrasound (EUS) guided fine-needle aspiration (FNA). EUS-guided FNA is gaining wider acceptance as the primary tool for evaluating abdominal lymphadenopathy and deep-seated lesions in proximity to the gastrointestinal tract.[3]

The celiac ganglia may be difficult to distinguish from celiac lymph nodes by CT or ultrasound imaging, and thus may be sampled during FNA evaluation of the celiac lymph nodes.[4] Few studies have described the cytomorphologic features of celiac ganglia.[5-7] However, to the best of our knowledge, there have been no reports about the frequency of celiac ganglia diagnosed by FNA. The aim of this study was to determine the frequency of detection and to characterize the cytologic findings of celiac ganglia diagnosed by image-guided FNA.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, our pathology database was retrospectively searched for all image-guided FNA cases involving the celiac region over a 14-year period (2000–2014). Only cases in which ganglion material was reported were further analyzed. All the celiac cases were not re-examined. Patient and clinical details in this subset of cases were documented, and all cytology slides reviewed. Per our standard protocol, all biopsies were performed by a radiologist or radiology physician assistant for CT or ultrasound-guided FNAs, or a gastroenterologist with training in endoscopy to perform EUS-guided FNA. In addition, these cases are routinely evaluated by the cytopathology team for immediate assessment of adequacy. At the time of the on-site evaluation, direct aspirate smears were prepared to make air dried and alcohol fixed slides. Air-dried smears were stained with Diff-Quik and alcohol fixed slides with the Papanicolaou stain. Cell blocks fixed in formalin were also made and sections stained with hematoxylin and eosin, and if needed utilized for immunohistochemistry.

RESULTS

Study population

During the study period, a total of 354 patients underwent FNA of a targeted area in the intra-abdominal celiac region. Celiac lymph nodes were targeted in 334 (95%) patients and in 20 (5%) cases, FNA was used to sample a celiac mass. Ganglion cells were identified in only 9 (2.5%) of these patients and these were all seen in EUS-guided FNA cases performed after 2008. These 9 patients (5 male, 4 female) were of average age 72 years (range: 57–85 years). FNA in these 9 cases specifically targeted a suspected celiac lymph node (7 cases; 80%), celiac axis soft tissue mass (1 case), and in one patient a supposed ganglion that measured 5 mm × 3 mm on imaging (1 case). The patient with a mass around the celiac axis presented with marked abdominal pain after a Whipple procedure for pancreatic cancer. None of these cases had a false positive on-site adequacy assessment or final misdiagnosis.

Cytologic findings

The aspirates in the 9 reviewed cases were mostly hypocellular, bloody, and had no lymphoid elements. Large epithelioid shaped ganglion cells were seen either sparsely dispersed [Figure 1] or cohesive in clusters [Figure 2]. When clustered the ganglion cells had a tendency to be more peripheral in these groups while nerve fibers were more central. The ganglion cells had low N:C ratios, granular cytoplasm with neuromelanin, and eccentric small round nuclei with prominent nucleoli. With the Papanicolaou stain, ganglion cell cytoplasm stained light blue/green with coarse brown granules [Figure 3]. With Diff-Quik, the pigmented granules were dark blue-purple. Nerve fibers consisted of wavy spindled cells [Figure 4]. On cell block, ganglion cells had similar voluminous pink cytoplasm and blue coarse granules [Figure 5]. Immunohistochemistry performed in one case showed S100 positivity of the ganglion tissue [Figure 6]. The patient who presented with a recurrent celiac axis mass after pancreatic surgery had concomitant pancreatic adenocarcinoma and ganglion cells in the FNA [Figure 7].

DISCUSSION

Review of the pathology literature reveals limited reports of celiac ganglia diagnosed by image-guided FNA.[5-7] Ours is the first study that reports the frequency of detecting celiac ganglia by FNA, based on data from our institution. These data indicate that the detection of

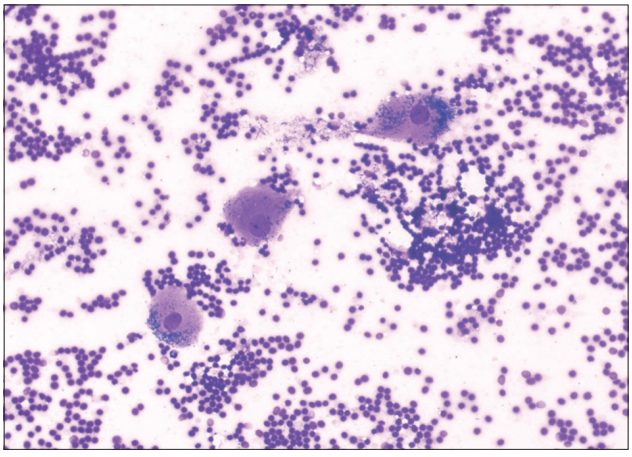

Figure 1: Fine-needle aspiration smear showing dispersed ganglion cells and a bloody background. Note the distinct darkly stained coarse cytoplasmic neuromelanin substance in these cells (Diff-Quik, ×200)

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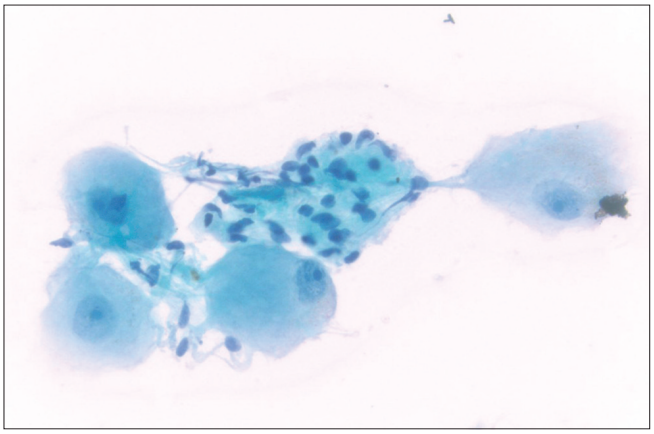

Figure 2: Cluster of ganglion cells characterized by large epithelioid cells with low N:C ratios, round nuclei, and distinct nucleoli. In addition, there are wavy, comma-shaped nuclei of probable nerve sheath origin in the center of the image (Papanicolaou, ×400)

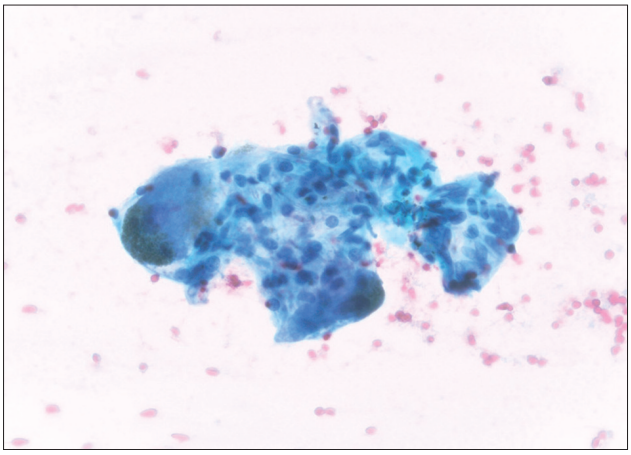

Figure 3: Ganglion cells are characterized by their brown cytoplasmic neuromelanin pigment granules (Papanicolaou, ×400)

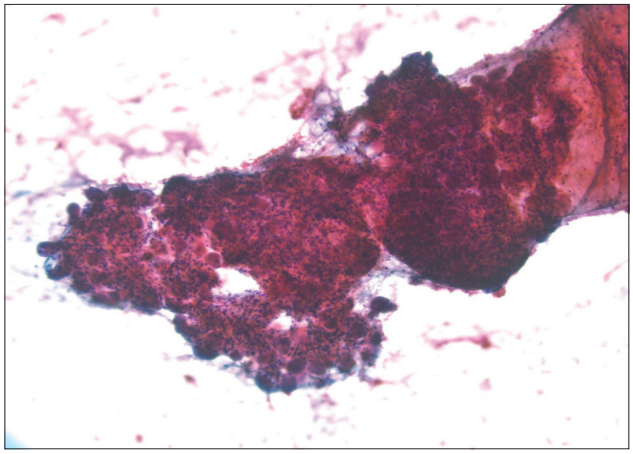

Figure 4: When intact, clusters of aspirated ganglion cells are located more peripheral to attached central nerve fibers (Papanicolaou, ×100)

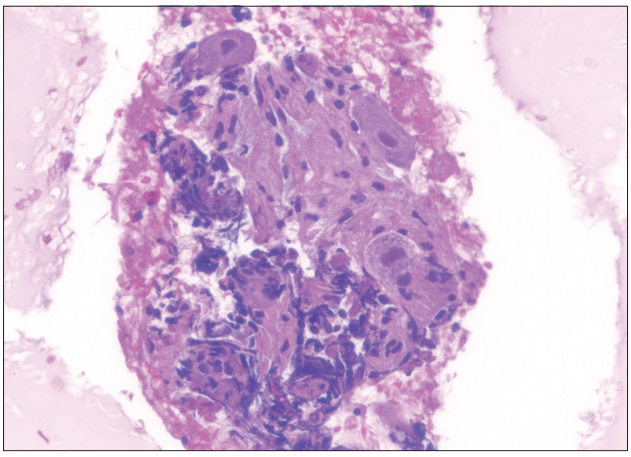

Figure 5: Cell block section of a celiac ganglion containing large ganglion cells and nerves (H and E, ×400)

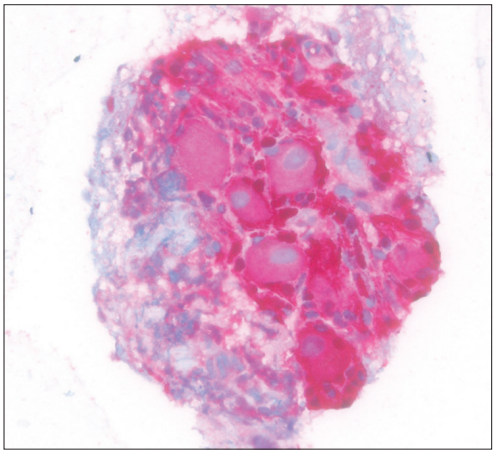

Figure 6: S100 positive celiac ganglion (immunohistochemistry, ×400)

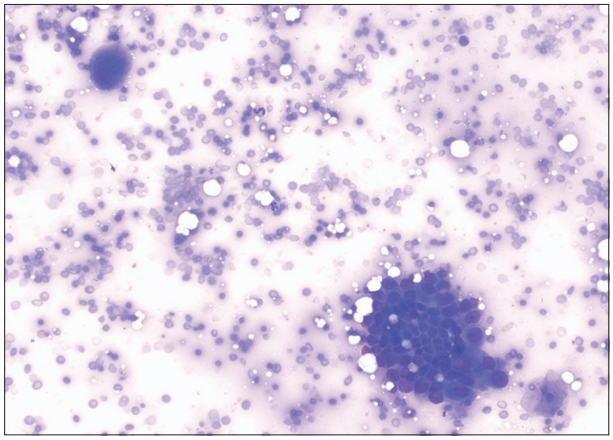

Figure 7: Fine-needle aspiration showing a ganglion cell in the upper left of the image associated with a group of pancreatic adenocarcinoma cells in the lower right of the image (Diff-Quik, ×200)

ganglion cells in image-guided FNA of the celiac region is infrequent (2.5%). It is possible that we may have detected more cases with ganglion cells in our series if all 354 cases were re-screened. Nevertheless, the low incidence in our

study is in accordance with data published by radiologists and endoscopists who similarly report only a few cases of celiac ganglia being inadvertently sampled during biopsy of celiac nodes.[4,8,9] Celiac ganglia are more likely to be visualized during EUS-guided procedures than with abdominal imaging. This may explain why all our cases were procured during EUS-guided FNA. On EUS, celiac ganglia are hypoechoic oblong or multilobulated structures with an irregular edge.[4] Echo-poor threads may be seen extending from ganglia, connecting one ganglion to another in a chain. Although it may be difficult to differentiate ganglia from nodes based on sonographic appearances alone, celiac nodes are often located somewhat more anteriorly than celiac ganglia. Celiac nodes also generally do not have irregular margins, and they do not appear in a chain.[9]

The indications for performing an FNA of the celiac ganglia are relatively limited. As demonstrated in our study, these ganglia are most often unintentionally biopsied during the workup of a patient with cancer (pancreatic or esophageal) to exclude celiac lymph node metastases. In prior reports, celiac ganglia have also been sampled to diagnose amyloidosis and viral infection.[10,11] In our patient where a celiac axis mass was targeted, the presence of recurrent pancreatic adenocarcinoma involving the celiac ganglion likely accounted for this patient's abdominal pain. Levy *et al*. reported similar involvement of abnormal celiac ganglia with pancreatic adenocarcinoma in 2 out of 6 patients.[12]

Albeit a rare finding, given that EUS-guided FNAs are quite common in today's practice, it is important that cytologists are aware of this possibility and can recognize the cytomorphologic features of these ganglia. Our review shows that aspirates of celiac ganglia are likely to be of low cellularity and bloody. If a suspected celiac lymph node was targeted, absence of lymphoid elements should raise the possibility that a ganglion was sampled, which may prompt the performer of the biopsy to see if the targeted lesion was actually sampled. Ganglia consisting of large ganglion cells and accompanying nerves may show varying cellular patterns, including cohesive clusters and/or isolated cells. Benign ganglia should not exhibit cellular atypia. However, the presence of large epithelioid ganglion cells with a prominent nucleolus may at first be alarming. Close inspection should reveal the characteristic low N:C ratio, bland nuclear morphology, and neuromelanin or lipofuscin-like substance (pigment) of these cells.

The morphologic differential diagnosis of celiac ganglia may include several entities. This includes reactive lesions (e.g., histiocytic or hemosiderin-laden granulomatous inflammation, reactive myofibroblastic proliferations such as proliferative myositis) and neoplasms (e.g., melanoma, neurogenic tumors, peripheral neuroblastic tumors, granular cell tumor, rhabdoid tumor, alveolar soft-part sarcoma, germ cell tumor such as seminoma, and Hodgkin lymphoma with a predominance of Reed–Sternberg cells). Melanoma cells may similarly have abundant cytoplasm, melanin pigment that resembles neuromelanin substance and nuclei with prominent nucleoli. However, unlike melanoma ganglion cells lack significant nuclear atypia and are unlikely to display multinucleation. Due to their epithelioid appearance, ganglion cells have to be distinguished from carcinoma including adenocarcinoma, anaplastic or undifferentiated carcinoma. Carcinoma cells will have more nuclear atypia. While ganglion cells may also mimic Reed–Sternberg cells in Hodgkin lymphoma, aspirates in these cases are more likely to be cellular with background reactive lymphoid elements. Finally, it may be difficult to distinguish ganglioneuroma from celiac ganglia based on morphology alone. If the clinical history and imaging findings are concerning for a diagnosis of ganglioneuroma, the differential diagnosis should include this possibility if ganglion cells are present. In ganglioneuroma, the mature ganglion cells are often multinucleated and may contain melanin pigment. The presence of neuromelanin may be less apparent in ganglioneuromas.[13] If ganglion cells are detected, it is important to ensure that there is no accompanying neuroblastomatous component, which would be diagnostic of ganglioneuroblastoma. Ganglioneuroblastoma may also contain melanin pigment.[14] As shown in one case of our study, ganglion cells and nerve fibers can be confirmed with S100 immunopositivity.

In summary, the finding of any benign ganglion material in an FNA sample from the celiac region is infrequent, but may be encountered during an EUS-guided procedure. Recognition of such celiac ganglia in these aspirates is important to avoid a potential diagnostic pitfall. These ganglia may be the cause of a mass-like lesion that was the target of the biopsy, but notifying the proceduralist of this finding during the FNA is important for correlation to make sure that the targeted lesion was not missed with inadvertent sampling of the celiac ganglia.

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AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors contributed to this article and approve of its publication.

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Frequency and characterization of celiac ganglia diagnosed on fine-needle aspiration
Ehab A. ElGabry, *MD*, Sara E. Monaco, *MD*, Liron Pantanowitz, *MD**

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David Chhieng, M.D.
Martha Bishop Pitman, MD
Andrea Abati, MD- chair
Andrew Fischer, MD
Zubair Baloch, MD

Scientific Program Committee

This Committee shall be responsible for design, organization, and conduct of the scientific meetings and other educational efforts of the Society. This committee will also seek to develop companion scientific programs at other national and regional pathology societies. These include:

- Companion Scientific Session at USCAP Annual Meeting
- Companion Educational Lunch Session at ASC
- Companion Scientific Session at ASCP
- Collaborate in Annual Papanicolaou Cytopathology Course- as needed

Zubair Baloch, MD (chair)
Matthew A. Zarka, MD
Rana Hoda, MD
Susan D. Rollins, MD
Esther Diana Rossi, MD, PhD
Nicole A. Massoll, MD
Andre L. Moreira, M.D., Ph.D.
Liron Pantanowitz, MD
Deb Chute, MD
Tarik Elsheikh, MD
David Chhieng, MD

Nominating Committee

The Nominating Committee shall consist of the three (3) immediate Past-Presidents of the Society. The most immediate Past-President of the Society shall be the Chair of this Committee. The Nominating Committee shall submit the names of nominees to offices elected by the membership (President-Elect, Secretary, Treasurer and members at large positions). Nominees for President-Elect, Secretary and Treasurer should have preferably served on the Board of Directors. Any member of the Society may submit nominations to this Committee for consideration. The Nominating Committee shall make its recommendations to the Board of Directors at least ninety (90) days before the Annual Meeting at which they are to be considered.

The Nominating Committee shall make at least two (2) nominations for President-Elect and at least one (1) nomination for each of the remaining positions on the Board of Directors eligible to be filled by vote of the voting members.

The report of the Nominating Committee will be submitted at least thirty (30) days prior to the next Annual Meeting to the voting membership, and election will be by majority vote of the voting members by mail/Fax/e-mail ballot.

Zubair Baloch, MD (Chair)
Andrea Abati, M.D
Binnur Onnul, MD
Martha Pitman, MD
Tarik Elsheikh, MD

L.C. Tao Educator of the Year and Yolanda Oertel Interventional Cytopathologist Awards Committee

Lester J. Layfield, M.D. (Chair)
Oscar Lin, MD
Philippe Vielh, M.D., Ph.D.
Fernando Schmitt, MD
Andrea Abati, M.D.
Dan Kurtycz, M.D.
Jordan Reynolds, MD

Budget and Finance Committee

- The committee shall work with the Treasurer to ensure the financial stability of PSC.
- Receive requests for budget allocations from PSC Committees and Task Forces.
- Prepare an annual budget for the ensuing year for review and approval by the Board of Directors.
- Recommend to the Board of Directors change in fees for the membership in collaboration with the chair of membership committee.
- Submit a financial report to the Board of Directors.
- Annually report on the finding of the end-of-year audit by a Certified Public Accountant.
- The committee shall be composed of a Chair, 4 members, and the Treasurer as *ex officio.*

Eric J. Suba, MD (Chair)
Massimo Bongiovanni, M.D.
Michelle, Reid, MD
Sara Monaco, MD
Britt-Marie Ljung, MD

Research Committee

- The committee obtains from USCAP a listing of abstract proposals that have been already accepted by USCAP for its annual national meeting.
- The Committee reviews and scores/ranks ***abstracts submitted by first authors in training in the category of "Cytopathology"***.
- The research committee chooses a "first place" and "second place" research awards to pathologists-in-training (residents and fellows) at USCAP meeting, on an annual basis.

Jennifer Brainard, M.D. (Chair)
Edmund Cibas, M.D.
Phillip Bomeisl, D.O.
Claire W. Michael, M.D.
Vinod Shidham, M.D., FRCPath, FIAC
Philippe Veilh, M.D.. PhD.
Qing Kay Li, M.D. Ph.D.
Paolo Gattoso, M.D.
Jay Wasman, MD
Aziza Nassar, MD

PSC Committees, 2015-2017

International Scientific Program and Relations Committee

- This committee will focus on developing companion scientific programs with international pathology societies and organizations.
- It will also foster strong relationships with pathology organizations as well as organizations which focus on providing / improving the quality of much needed basic cytology screening services and education.

Fernando Schmitt, M.D. (Chair)
Andrew Field, MD
B Cochand-Priollet, MD, MIAC, PhD
Eric J. Suba, M.D.
Philippe Vielh, M.D.
Salwa El-Haddad, MD
Lester J. Layfield, MD
Guido Fadda, MD
Binnur Önal, MD,FEBP,FIAC
Ravi Mehrotra, MD, PhD, FRCPath
Ben Yang, MD
Tarik Elsheikh, MD

Membership Committee

- The Membership Committee shall perform such duties as directed by the Board of Directors to increase membership roster and further the Society's goals of its members.
- The committee shall screen and approve new members and will work closely with the secretary treasurer to keep and maintain an updated list of all the paid members of the society.
- This committee is also in-charge of making sure that all paid members have access (print and online) to the current and the future line up of journals affiliated with PSC.

Claire Michael (Co-chair, USA and Canada)
Esther Diana Rossi, MD (Co-chair, International)
Angelique W. Levi, M.D.
Tamar Giorgadze, MD
Momin Siddiqui, MD
Beatrix Cochand-Priollet, M.D.
Michael Yang, MD
Sule Canberk, MD

Newsletter and Publication Committee

- This Committee shall assist in the publication of reports and documents generated by the standing committees.
- It shall maintain the publication of a regular newsletter to keep the membership informed of all activities.
- The Newsletter editor shall be the chair of the committee.

Vinod B. Shidham, M.D. (Chair and Editor of Focus)
Oscar Lin, MD
N. Paul Ohori, M.D.
Adebowale J. Adeniran, M.D.
Aziza Nassar, MD

Education and Training Task Force

- This committee evaluates the effectiveness of the overall PSC CME and CE Programs with scientific program committee.
- The Committee is also responsible for reviewing the evaluations from the PSC educational activities and relaying any topics, changes, or improvements for the overall CME Program to scientific program committee.
- The members of this committee are also responsible for soliciting educational content for pathology trainees (residents and fellows) for the PSC newsletter.

Rana Hoda, MD- (Chair)
Aylin Simsir, M.D.
Gordon Yu, MD
Darshana Jhala, MD
Joan F. Cangiarella, M.D.
Guoping Cai, M.D.
Andre L. Moreira, M.D., Ph.D.
Malini Harigopal, MD
Xin Jing, MD
Fadi Abdul-Karim, MD

Standards of Practice Task Force

Standards of practice in cytopathology is an important area which needs to be addressed on a continual basis. This committee will work on developing standards of practice and guidelines for cytopathology using a variety of methodologies and resources, The parameters when developing these standards of practice include but are not limited to professional knowledge, application of methodologies and guidelines in practice, formal scientific presentations and discussions, learning and assessment and ongoing professional development.
The standard of Practice task force will:

- Initiate the process to discuss and define general principals, skills, values and issues that encompass the overall and daily practice of cytopathology.
- Once these recommendations and guidelines are drafted and posted on the PSC website, the committee will begin the process of review with feedback from discussion at scientific sessions and website feedback.

Zubair Baloch, M.D. (Chair)
Lester J. Layfield, MD
Rana Hoda, MD
Martha Bishop Pitman, MD
Tarik Elsheikh, MD
Fadi Abdul-Karim, MD

PSC Website Committee

- Manage the web presence of PSC by developing and maintaining web content describing PSC and its mission
- Revise the PSC webpage to update latest information with any committee or the executive board
- Design and implement web content and other educational services that comply with the accessibility standards
- Coordinate with PSC newsletter committee to post and archive newsletters
- Support web presence of any PSC committee by posting, developing or managing appropriate and relevant content

Liron Pantonowitz, MD (Chair)
Dan Kurtycz, M.D.
Sara Monaco, MD
Scott Anderson, MD
Sepi Mahooti, MD
Brian Collins, MD
Daniel Cowden, MD


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Martha Bishop Pitman, M.D.
President, PSC

Eric Suba, M.D.
Treasurer, PSC

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