

# 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



I am delighted to invite Gordon H. Yu, M.D. as the guest editor for the December 2013 issue of Focus. I welcome the active participation by the incoming editorial board members including the new section- 'Images in Cytology' by Dr. Giorgadze.

The Focus editorial board is also thankful to the PSC members for their timely contributions. We are looking forward to your future proactive contributions.

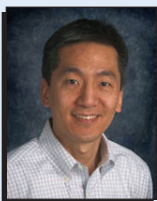
Please enjoy the issue!

Sincerely,

Vinod B. Shidham, MD, FRCPath, FIAC

## From the Guest Editor's Desk

Gordon H. Yu, M.D.



Welcome to the current issue of the FOCUS newsletter. I would like to thank Dr. Vinod Shidham for the opportunity to serve as Guest Editor of this issue and express my sincere appreciation to all of the authors for their efforts and contributions that follow.

The Timely Topics section includes two contributions, the first from Dr. Aziza Nassar of the Mayo Clinic in Jacksonville, Florida, who provides a valuable review and summary of the evaluation of pancreatic cyst fluid aspirates, including cytomorphologic

Con't on page 2

## President's Message

Zubair W. Baloch, MD, PhD



*Teamwork is the ability to work together toward a common vision. The ability to direct individual accomplishments toward organizational objectives. It is the fuel that allows common people to attain uncommon results.*

~ Andrew Carnegie

The year 2014 is shaping up to be an exciting year for Papanicolaou Society of Cytopathology (PSC). This year PSC welcomed two new members to the executive board; Dr. Momin Siddiqui was elected as secretary and Dr. Claire Michael as members at large. Dr. David Chhieng rotated off from the position of secretary after two consecutive terms amounting to 4 years. David has volunteered many hours working for PSC; he was given a standing ovation by past and present members of the PSC executive board. I am honored to have served with him on the executive board and hoping that after a short hiatus he will be back to serve as an officer of PSC.

Con't on page 2

## Editorial Board Members

**Ricardo Lastra, MD**

University of Pennsylvania Medical Center  
[Ricardo.lastra@uphs.upenn.edu](mailto:Ricardo.lastra@uphs.upenn.edu)

**Oscar Lin, Md PhD**

Memorial Sloan Kettering Cancer Center  
[lino@mskcc.org](mailto:lino@mskcc.org)

**Aziza Nassar, M.D.**

Mayo Clinic, Jacksonville, Florida  
[nassar.aziza@mayo.edu](mailto:nassar.aziza@mayo.edu)

**N. Paul Otori, M.D**

University of Pittsburgh Medical Center  
[ohorinp@upmc.edu](mailto:ohorinp@upmc.edu)

## IN THIS ISSUE

From Editor's Desk	.....1
President's Message	.....1
Timely Topics	
Cytology Without Borders	.....3
Pancreatic Cyst Analysis	.....8
Case Report	.....11
Images in Cytology	.....15
News and Announcements	.....16

## Membership Application

(Please download, print and complete)

<http://www.papsociety.org/docs/09/pscapp2009.pdf>

## Focus is published by the Papanicolaou Society of Cytopathology

### Editor:

**Vinod B. Shidham, MD, FRCPath, FIAC**  
 Wayne State University School of Medicine  
 Karmanos Cancer Center, & DMC  
[vshidham@med.wayne.edu](mailto:vshidham@med.wayne.edu)

### Associate editor:

**Adebowale Joel Adeniran, M.D.**  
 Yale University School of Medicine  
[adebowale.adeniran@yale.edu](mailto:adebowale.adeniran@yale.edu)

### Editorial office:

Vinod B. Shidham, MD, FRCPath, FIAC  
 Professor & Vice-chair, Dept of Pathology,  
 Wayne State University School of Medicine,  
 Karmanos Cancer Center, & DMC  
 Old Hutzel Hospital (Dept of Cytology-  
 Ground Floor),  
 4707 St. Antoine Blvd  
 Detroit, MI 48201  
 Ph: (313) 745 0831  
 (Kathy Rost Assistant to Dr. Shidham)  
 Fx: (313) 745 7158

## From the Guest Editors Desk

examination and the utilization of various biochemical and molecular markers. In a second article, Dr. Andrew Field of St. Vincent's Hospital in Sydney, Australia (and past President of the Australian Society of Cytology) provides a look into the admirable efforts that he and others have made to bring the benefits of fine needle aspiration biopsy to the population of sub-Saharan Africa in "Cytology Without Borders: Activities in Teaching Cytology in Sub Saharan Africa."

An interesting Case Report is provided by Dr. Ricardo Lastra, Cytopathology Fellow at the University of Pennsylvania, which illustrates the importance of recognizing subtle cytomorphologic clues, leading to a correct diagnosis. Finally, Dr. Tamar Giorgadze,

from New York Presbyterian Hospital/Weill Cornell Medical College has kindly provided two images for the newly-established Images in Cytology section.

Many thanks again to all of the contributors, Dr. Shidham and Dr. Zubair Baloch for his continued vision and outstanding leadership of the Society.

Sincerely,

**Gordon H. Yu, M.D.**

*Guest Editor*

## President's Message

The 2014 PSC presentations at United States and Canadian Academy of Pathology (USCAP) began with the International Relations Committee Afternoon Session moderated by Dr. Eric Suba. The presentations included, **Introduction to The IAC Project: Results from the Papanicolaou Society's Global Delphi Exercise for Cervical Cancer Prevention** given by Dr. Eric Suba. Dr. Philippe Vielh, the current president of International Academy of Cytology spoke on **The IAC Project: Bringing Cervical-Vaginal Screening to Resource-Constrained Settings throughout the World** followed by Dr. Stephen Raab highlighting the basic needs and framework of **Internet-based Cytology Training**. These presentations were very informative and confirmed that we all practice cytopathology in the age of "globalization". The presenters highlighted the concept that cytopathology education and practice is devoid of any boundaries and can be an exciting undertaking.

The PSC annual cocktail reception was very well attended and it was great to see all the friends and well-wishers of the society. The PSC then presented its Companion Society Evening Session. Prior to the scientific presentations, a brief awards ceremony occurred in which **Dr. Marluce Bibbo** received the **PSC Lifetime Achievement Award**. **Dr. Hormoz Ehya** received the **L.C. Tao Educator of the Year Award** and **Dr. Paul Wakely** was honored with the **Yolanda Oertel Interventional Cytopathologist of the Year Award**. The resident research award winners were first place Dr. Lisa Rooper - from Johns Hopkins University Hospital, Baltimore, Maryland and second place Stephen J. Bloechl from University of Minnesota, Minneapolis, MN.

The PSC Scientific Program at this 103rd USCAP meeting was titled **"Reinventing Our Profession: Challenges and Experiences"**. Presentations were given by Drs. Britt-Marie Ljung and Susan Rollins on the topic of ultrasound-guided FNA performed by pathologist in both academic and community settings. Dr. Yuri Nikiforova discussed the molecular analysis of thyroid FNA specimens and closing the knowledge gap on molecular profiling of thyroid tumors. Dr. Dara Aisner discussed the emerging technologies and new molecular markers applied to lung cytology specimens with an emphasis on how cytology smears can serve as a reliable resource for molecular analysis. The session ended with a presentation from Dr.

Liron Pantanowitz on next generation sequencing and current biomedical informatics challenges.

**In the spirit of fostering relationships with other pathology societies** PSC had its first companion session with Binford Infectious Disease Society. I took the privilege of asking **Dr. Kathleen Montone**, who serves on the board of Infectious Disease Society to provide us with an account of this co-sponsored session. As per Dr. Montone "On Sunday, March 2, 2014 at the 103rd Annual Meeting of the United States and Canadian Academy of Pathology in San Diego, California, a co-joint companion meeting of the Binford Dammin Society of Infectious Disease Pathologists and the Papanicolaou Society was held. Organized by Drs. Andre Moreira (BD Society) and Zubair Baloch (President of the Papanicolaou Society), the combined meeting discussed the role of Cytopathology in Infectious Diseases. Dr. Pamela Michelow from University of the Witwatersrand and National Health Laboratory Service Johannesburg, Gauteng, South Africa started off with a lecture on the "Role of Cytology in the Diagnosis of Infectious Diseases in a Developing Country: The South African Experience" followed by Dr. Andrew Field of St. Vincent's Hospital in Sydney, Australia who spoke on the "Role of Fine Needle Biopsy in the Diagnosis of Infectious Diseases". Dr. Moreira of Memorial Sloan Kettering discussed "Infectious Disease in a Cancer Center, Mimickers and Complications in the Immunocompromised Host". The session was rounded out with a talk by Steve C. Schmechel, MD, PhD, University of Washington Medical Center, Seattle, WA who spoke on "Molecular Applications for the Diagnosis of Infectious Diseases in Cytological Material". The session was very well attended by both societies and led to excellent discussion. In addition, the overall program was deemed to be a topic for the upcoming IAP Meeting to be held in Brisbane in 2015! Thank you all for attending this first joint meeting between these two societies. We hope to present more sessions like this in future USCAP meetings".

To conclude I am of that belief that PSC **"a society with big heart"** with its committed executive board and members is on its way to be a cytopathology society that values open communication, collaboration and sharing of resources; and will take strong roots in global level.



## Cytology Without Borders: Activities in Teaching Cytology in Sub Saharan Africa

### Dr. Andrew Field

Associate Professor Notre Dame University Medical School,  
Deputy Director and Senior Consultant, St. Vincent's Hospital  
Sydney Australia

Since January 2007, Dr. Andrew Field from Sydney, along with faculty members Dr. William Geddie from University Health Network, Toronto and Dr. Matthew Zarka from the Mayo Clinic, Scottsdale, has organized and provided Fine Needle Aspiration Biopsy (FNB) tutorials in sub Saharan Africa. Andrew and Bill met at a tutorial at the Karolinska Hospital in 1989 run by Dr. Torsten Lowhagen and his colleagues Edna Tani and Lambert Skoog, and Matthew trained there for a period of time in the 1990s, and met Andrew at the memorial Symposium celebrating Torsten Lowhagen's life in 1999. Dr. Lowhagen was an inspiring teacher of FNB technique and cytological diagnosis.

In October 2006 at the International Academy of Pathologists (IAP) Congress in Montreal at an all day symposium on providing pathology in resource-poor countries, Dr. Field presented a talk on the potential role of cytopathology in diagnosing infections in developing countries. At a subsequent session he was invited by Dr. Michael Odida from Makerere University to organize and teach at a FNB tutorial in Kampala, Uganda. He asked Dr. Geddie to join him.

This first weeklong tutorial was provided in January 2007, at the Mulago Hospital and Makerere University in Kampala, Uganda, under the auspices of the Papanicolaou Society of Cytopathology. Since that time Dr Field has organized and taught at a total of 12 tutorials in sub Saharan Africa, along with fellow faculty, Dr. Geddie and Dr. Zarka. The tutorials are based on the cytopathology training and teaching experiences of more than 30 years of each of the three cytopathologists, and have a similar emphasis on the basic need for excellent performance of the FNB and direct smear that Dr. Lowhagen taught.

Each tutorial has involved delivering didactic lectures and interactive case based tutorials by Powerpoint presentations to overcome any lack of teaching infrastructure. The teaching is from 9am to 5pm, over four to four and a half busy days, and strongly emphasizes practical hands-on training in FNB and smear making technique using bananas as FNB targets and hand lotion as the smearing material, and demonstrations in FNB clinics. The tutorials to date are listed here:

1. January 2007 Makerere University and Mulago Hospital, Kampala, Uganda (Drs. Geddie and Field)
2. October 2007 Lagos University Teaching Hospital, Lagos,

Nigeria (Drs. Geddie and Field)

3. January 2008 Muhimbili University of Health and Allied Sciences, Dar Es Salaam, Tanzania (Drs. Zarka and Field)
4. October 2008 Aga Khan Hospital, Nairobi, Kenya (Drs. Geddie and Field)
5. September 2009 Kenyatta and Aga Khan Hospitals, Nairobi, Kenya (Drs. Field and Mina Desai)
6. October 2009 Muhimbili University of Health and Allied Sciences, Dar Es Salaam, Tanzania (Drs. Field and Mina Desai)
7. May 2010 Stellenbosch University and Tygerburg University Teaching Hospital, Cape Town, South Africa (Drs. Geddie, Field, Zarka and Colleen Wright and colleagues)
8. May 2010 Aga Khan Hospital, Nairobi, Kenya (Drs. Geddie, Field and Zarka)
9. September 2011 Muhimbili University of Health and Allied Sciences, Dar Es Salaam, Tanzania (Drs. Geddie, Field and Zarka)
10. January 2013 Black Lion University Teaching Hospital, Addis Ababa, Ethiopia (Drs. Geddie and Field)
11. December 2013 Black Lion University Teaching Hospital, Addis Ababa, Ethiopia (Dr. Field)
12. January 2014 University of Stellenbosch and Tygerberg University Teaching Hospital, Cape Town, South Africa (Dr. Andrew Field, and Allan Wilson from Scotland and Nick Dudding from Sheffield)

Drs. Geddie and Field also attended two meetings of pathologists at the Lagos Tutorial at which discussions were held and the West African Society of Cytology was established in 2008. Dr. Field attended similar meetings in Nairobi and Dar Es Salaam, in September and October 2009, when discussions between pathologists from Kenya, Uganda and Tanzania, were held to try and establish an East African Cytology Society. Dr. Field has also lectured at the APECSA Congress in Mombassa, Kenya, in early October 2008; provided a two day pre

Congress FNB tutorial with Dr. Mina Desai and spoke at the inaugural scientific meeting of the West African (Anglophone) Society of Cytology in April 2009 Kano, Nigeria, followed by two days of lectures and demonstrations at each of Lagos State University Teaching Hospital and Ibadan Medical College Hospital over the following week; organized a Gynecological and Fluids tutorial at Makerere University, Kampala, July 2009, provided by two other stalwarts of the Papanicolaou Society, Drs. David Chhieng and Tariq Elsheikh; provided a two day FNB tutorial for a British Division of the IAP Combined Breast Cytology and Surgical Pathology Tutorial with Drs. Ian Ellis and Sarah Pinder, held before the APECSA Congress at which the College of Pathologists of East, Central and Southern Africa (COPECSA) was established, in Kampala, Uganda, September 2009; and provided two days of lectures and demonstrations on FNB cytology at the Lilongwe Referral Hospital, Malawi, September, 2012.

The tutorials and these other activities are attempting to meet the challenges of teaching and developing cytopathology in sub Saharan African countries.

## **Current Problems in Providing Pathology Services in Sub Saharan Africa**

In sub Saharan Africa countries there are a small number of pathologists with few full-time cytopathologists, and an even smaller number of cytotechnologists, working within a limited medical infrastructure with few and poorly supported laboratories, which are inadequately funded and equipped. There is a shortage of well-trained cytopathologists to provide a service, as well as, teach and mentor trainees, and there is a shortage of cases for supervised reporting and cytology teaching. There is a lack of funding for the laboratories, and for a reliable and inexpensive internet, electronic teaching aids, text books and journals, and for funds available to attend meetings and conferences.

Pathologists from developing countries who have been trained and been accredited in Europe or North America tend not to return, which further worsens the undersupply of pathologists in their native countries. If these pathologists do return, they struggle to apply their new expertise because of a lack of laboratory and clinical infrastructure in the public and fledgling private systems, and they frequently are diverted into better paid international agencies. There is a need to establish post graduate medical education programs and opportunities to specialize and achieve better income streams to retain more pathologists.

There is a fundamental need for a strong core of medical graduates and other health care workers crucial to provide high level medical care, teaching, leadership and advice to government. Recently the number of medical graduates and trainee pathologists has been increasing across most medical colleges in sub Saharan Africa, but there has been no apparent increase in the number of teachers or the infrastructure required.

## **Possible Solutions**

Cytology, especially FNB, is a powerful diagnostic tool in all medical environments and in the developed world can provide not only a rapid cytomorphological diagnosis but also material for a wide range of sophisticated ancillary tests including flow cytometry, immunohistochemistry and molecular studies. This is exemplified by the role of EBUS FNB in diagnosing and staging lung cancer, and providing material for ancillary testing including EGFR FISH. FNB provides a rapid and accurate diagnosis with immediate triage, and is minimally invasive, cost effective, and requires minimal equipment and laboratory infrastructure.

FNB can triage and in most cases make a specific diagnosis in patients who fill expensive hospital beds or clog outpatient clinics waiting for incisional biopsies, so that appropriate treatment can be commenced. FNB of a mid cervical mass in a 40 year old patient can diagnose and distinguish mycobacterial infection, a reactive lymph node, HIV related lymphadenopathy, high grade lymphoma, metastatic squamous cell cancer or a branchial cyst, and replace expectant treatment for tuberculosis in an environment of multi resistant disease.

These major benefits are massively accentuated in medically resource-poor countries where the lack of histopathology laboratories makes the immediate role FNB can play so potentially crucial across all areas of medicine and surgery, in the diagnosis of any palpable lesion, including neoplastic diseases, adult and paediatric TB and other infections, and HIV positive patients with lymphadenopathy. FNB offers a similar impact in pathology diagnosis and therefore effective treatment, as mobile phones do in communication in these infrastructure poor countries. The FNB can be performed as an outpatient or hospital service or in 'up country' clinics. Of course, this requires a critical mass of well-trained cytopathologists to provide a diagnostic service as well as teach trainee pathologists and cytotechnologists.

To produce a rapid increase in trained cytopathologists in developing countries in sub Saharan Africa, a number of cytology-specific educational programs are required and can be run simultaneously, to supplement the dedicated pathologists practising and teaching cytopathology in these countries and the courses that have been run such as the Stellenbosch Cytopathology MSc of course by Professor Colleen Wright.

The cytopathology tutorials run by Dr. Field and the faculty in sub Saharan African countries aim to assist the cytology training of pathologists, trainee pathologists and cytotechnologists. These tutorials move from country to country minimizing the travel and accommodation costs of local registrants, and emphasize the technique of FNB, smear making and staining of high quality smears, as well as a practical approach to the diagnosis of palpable lesions. The aim is that cytopathologists achieve proficiency in performing



FNB and making smears, and so are empowered to return to their home countries and actually carry out FNB, so as to provide an immediate diagnostic service while gradually increasing their diagnostic experience and teaching role. The pathologists are based in their own practises with their own spectrum of disease, and the teaching is provided to as many pathologists as possible and not just to a select few trained in developed countries; for example, the 2008 tutorial in Dar Es Salaam attracted 15 of the country's 17 pathologists.

The cost to the local pathology community is kept to a minimum. There is a registration fee covering catering and perhaps a facility hire met by the local organisers, and so far the faculty have travelled at their own expense supported by their own institutions and on one occasion, the College of American Pathologists (CAP) Foundation, and on another by the Royal College of Pathologists of Australasia.

## **What else can be done to assist training sub Saharan African pathologists?**

Ideally, leading pathologists and trainees should be offered short intensive training periods or supernumerary 'sandwich fellowships' between 13 and 26 weeks in established diagnostic cytopathology laboratories, in South Africa, which unfortunately has limited teachers and funds available, or in developed countries. Potentially, experienced cytopathologists can work for periods of time in sub Saharan African laboratories, as one off visits, or on a roster, but in the past such pathologists were often used mainly by the local institution simply to provide a diagnostic service rather than as teachers. Also, local universities or hospitals or institutions such as COPECSA could establish courses, and faculty from developed countries could be brought in to assist local teachers.

Such programs are eminently suited to cytopathology, where the cost and infrastructure requirements to establish and provide a quality FNB service are low compared to surgical pathology services.

Internet training offers promise to many training programs in developing countries, but access is not readily or continuously available, and there are problems related to cost, downloads, connection speed and electricity supplies. Provision of quality up to date text books and recent hard copy journals such as *Diagnostic Cytopathology*, *Acta Cytologica* and *Cytopathology*, is essential for teaching and research. Dr. Lester Layfield, another Papanicolaou Society ex-president, has organized delivery of copies of *Diagnostic Cytopathology* to twelve key institutions in sub Saharan Africa over the last three years.

Telepathology either by static or continuous transmission of digitized images for primary reporting, does not train local pathologists, but can provide a mechanism for second opinions. It does require a local operator trained in cytopathology to perform the FNB, make the smears, provide adequate staining, and then to select images, and current scanners are not ideally suited to cytopathology and

require uninterrupted electricity and internet connections. It appears much more powerful to train a cytopathologist who can then provide the diagnostic service, as well as, teach and fulfill the multiple crucial roles that pathologists provide in their laboratories and hospitals.

Cytology laboratories can report cervical smears and assist in screening and diagnosis of cervical carcinoma, the most common carcinoma causing death in women in sub Saharan Africa. Possible HPV immunization programmes will still leave generations of sub Saharan African women exposed to cervical cancer, unless a cervical screening program can be put in place, and HPV testing requires the same screening program infrastructure as cervical smears.

Pathologists are poorly paid in the public sector in sub Saharan Africa, and training in cytopathology can allow them to run FNB clinics that not only benefit patients and the local medical system, but also generate private practise income. Pathology in many countries struggles to attract medical graduates into specialty training because of the cost of establishing a laboratory, and FNB requires minimal infrastructure. Finally, FNB can be used for preoperative and intraoperative diagnosis of lesions at surgery, as frozen sections are not available.

## **Challenges in FNB training in sub Saharan Africa**

Training and accreditation programs in cytopathology need to be established on a national basis or by organizations such as COPECSA, and may be better suited to a university-based system. Currently Dr. Field is in discussion with members of the executive board of COPECSA and the East African division of IAP to establish a program of tutorials.

On occasion teaching in pathology has encountered complex local situations with rivalries between individuals, hospitals and the public and private sectors, and training in any branch of pathology through 'safaris' or tutorials may upset the balance of the practice of cytopathology within a university teaching hospital department or in cities, challenging pathologists' practices or income. Disputes may also occur between laboratory technicians and cytopathologists as to who should run cervical smear reporting and screening programs.

The most significant problem apart from a lack of funding for pathology services and training and a failure by local departments of health to recognize the crucial role of pathology testing in the establishment and provision of health services, is the continuing civil and political unrest in many sub Saharan African countries.

## **Possible Sources of Funding**

Funding is required to assist pathologist teachers to travel to the tutorials, and importantly to bring registrants to the tutorials by assisting them with their travel and accommodation costs. The CAP Foundation supported the tutorial in South Africa in May 2010 with a grant.

Partly as a way to raise funds to support the tutorials, in June 2012 Dr. Field organized the First Sydney Advanced FNB Cytology Tutorial on the St Vincent's campus in the Garvan Institute Auditorium, and then ran the tutorial for the second time in July, 2013. A third tutorial has been organized for May 5 to 9th, 2014.

The faculty for the Advanced FNB Cytology Tutorials has included Drs. Geddie, Field and Zarka, as well as other members of the Papanicolaou Society: Dr. Martha Pitman, from Massachusetts General Hospital, Dr. Syed Ali from John Hopkins Hospital, Dr. Fernando Schmitt from Porto, Portugal and now Toronto, and Dr. Elizabeth Salisbury from Prince of Wales Hospital, Sydney.

In 2012 and 2013, the international and Australian faculty repeated the tutorials in Bangkok, where Dr. Sam Raengdeng of the Thai Society of Cytology provided the local organization. The aim is to foster cytology in Thailand and the surrounding countries. The Third Tutorial will be presented the week after Sydney, in Jakarta, Indonesia. The Sydney tutorials have raised significant funds which are now held in trust by the Royal College of Pathologists of Australasia, for the teaching of cytology in the developing world. In September 2012, the senior cytotechnologist from Bhutan was brought to Australia to attend the Australian Society of Cytology tutorial and meeting, and spent time in St Vincents and Adelaide Hospitals. Dr. Field had met him while performing a cytopathology service review of Bhutan with Thai colleagues in May 2012. In January 2014 at the tutorial at Tygerburg Hospital 21 registrants from Kenya, Tanzania, Uganda, Rwanda, Burundi and Namibia, were given financial assistance to travel to South Africa.

## Final Comments

The fundamental drive of the tutorials run by Drs. Field, Zarka and Geddie, and their colleagues is that the key to the improvement in cytology services is the training of sufficient cytopathologists and cytotechnicians to provide an immediate diagnostic service and to provide teaching material and training for an ever increasing number of cytology practitioners.

If a pathologist or trainee pathologist can be trained to perform a FNB and prepare direct smears using good technique, taught an approach to interpreting the slides and provided support with adequate textbooks and follow-up teaching at subsequent tutorials, then that individual can practise and teach and provide impetus to improve pathology diagnosis for their working lifetime. It should be possible to also provide these cytopathologists with a second opinion service using simple digital images and image transfer by an ever-improving internet. Current laboratory infrastructure and expensive equipment requirements in cytology are minimal, but, as in the developed world, the FNB technique can provide material now and in the future for the most sophisticated of immunohistochemical and molecular testing, when these become available in these developing countries.

Further tutorials have been planned for Maputo Hospital, Mozambique, where Drs Fernando Schmitt and Andre Moreira will present a tutorial in Portuguese, and Aga Khan Hospital in Nairobi in September 14 to 17, 2014.

Dr Field is interested in expanding the faculty and the number of tutorials held in Africa and elsewhere. The teaching environment can be challenging, and teaching at the tutorials requires the provision of didactic lectures and case-based tutorials (all in Powerpoint format), and a willingness to demonstrate the FNB technique and rapid on-site evaluation. Dr. Field is also looking for teaching centers that can provide 'sandwich fellowships' of one to six months for visiting senior residents or pathologists of developing countries to receive training as supernumerary trainees or fellows in cytopathology.

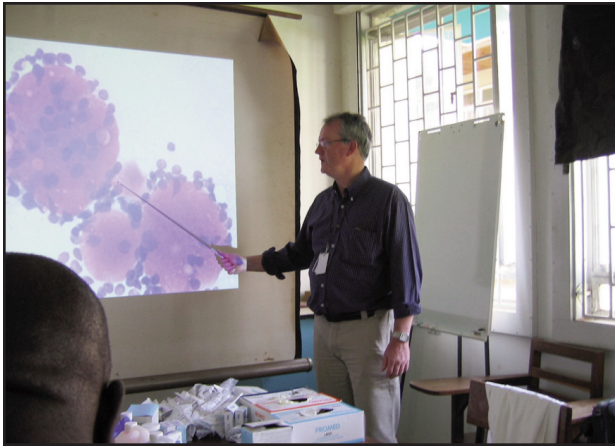
If your hospital or centre is interested in providing or assisting with the placement of these pathologists, please contact him by email at [afield@stvincents.com.au](mailto:afield@stvincents.com.au).

Drs. Geddie, Zarka and Field would welcome cytopathologists to attend the Third Advanced FNB Cytology Tutorial in Sydney. It is aimed at practicing cytopathologists, fellows and trainees in cytopathology; speakers try to challenge each other and the registrants with case-based tutorials, which are set at a more difficult level. Enquiries can be sent to Dr Field on [afield@stvincents.com.au](mailto:afield@stvincents.com.au).

## References

- Chen et al, A survey of Sub-Saharan African Medical Schools. Human Resources for Health, 2012;10:4-28
- Das DK. FNAC. Its origin, development and present status with special reference to a developing country, India. Diagn Cytopathol 2003;28:345-351.
- Field AS, Geddie WR, Zarka M, et al. Assisting Cytopathology Training in Medically under-Resourced Countries: defining the problems and Establishing Solutions. Diagnostic Cytopathology 2012;40:273-281
- Kaminsky DB. Into Africa: Cytology for one world. Acta Cytol 2008;52:399.
- Michelow P, Meyers T, Dubb M, Wright C. The utility of FNA in HIV positive children. Cytopathology 2008;19:86-93
- Suba EJ. Crossing the quality chasm: A requirement for successful cervical cancer prevention in developing countries. Clin Lab Med 2004;24:945-963
- Wright CA, Pienar JP, Marais BJ. FNAB: diagnostic utility in resource-limited settings. Ann Trop Paediatr 2008;28:65-70
- Sivasubramaniam V, Faduyile F, Zarka M, Deery A, Field AS. Maxillary cementifying fibroma: a case report highlighting the expanding role of e-Medicine in cytopathologist collaborations. Diagn. Cytopathol 2012;40:810-814

## Figure Descriptions



**Figure 1:** Dr. Field lecturing in Mulago Hospital in 2007



**Figure 2:** Dr. Zarka demonstrating FNB technique in Muhimbili Hospital in 2008



**Figure 3:** Dr. Field demonstrating FNB technique in Mulago in 2007



**Figure 4:** Dr. Geddie demonstrating FNB technique in Lagos University Teaching Hospital, 2007



**Figure 5:** Registrants with Dr. Field and Professor Ephata Kaaya, Muhimbili Hospital, 2008





## Pancreatic cyst fluid analysis and adjunctive utility of biochemical and molecular markers

**Aziza Nassar, MD, MPH, FIAC**

Mayo Clinic, Jacksonville, FL

Pancreatic cysts are a relatively common occurrence and, when small, are generally benign (1). They may be incidentally detected in up to 13.5% of patients (2), and approximately 1.2% of general medical patients have a pancreatic cyst that requires follow-up (3). Pancreatic cystic lesions (PCLs) include pseudocyst and neoplastic cystic lesions (1-3). The neoplastic cystic lesions include serous cystadenoma (SCA), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN) (1-3). Pseudocysts and SCA are nonmucinous and lack malignant potential, whereas MCN and IPMN are mucinous cysts with the potential of becoming malignant (precancerous lesions) (1). It is the latter entity that requires radiologic and biochemical follow-up for early detection of pancreatic cancer (1). Surgery carries a higher risk in older patients (especially those with multiple comorbidities), and if a precancerous cyst does not display malignant features, clinical observation is often favored over surgery (1). As a result, the need for long-term surveillance using radiologic imaging and biochemical markers in addition to cytology is critical.

The current modality for evaluating PCL often includes endoscopic, ultrasound-guided fine-needle aspiration (EUS-FNA) for cyst fluid analysis (1, 2, 4). Cyst fluid can be analyzed for tumor and biochemical markers (CEA, CA 19-9 and amylase respectively), cytologic evaluation and DNA abnormalities such as K-ras gene mutation and allelic imbalance (2, 4, 6). Pancreatic cyst CEA level is considered to be the most accurate tumor marker for diagnosing mucinous cysts (2). Approximately 0.2 to 1.0 mL of cyst fluid is required to perform this test, and a cut-off of 192 ng/mL can be expected to capture approximately 75% of mucinous cysts (2). The presence of a K-ras mutation is very specific for a mucinous cyst but lacks sensitivity, while cytologic examination may accurately establish a diagnosis of malignancy, typically in the presence of a solid component in the cyst (2). However, the sensitivity of cyst fluid cytology is also relatively low (32 -50%), due to the typically limited cellularity of aspirated cyst fluid (7).

Endoscopic ultrasound findings alone have an accuracy of 50% to 73% for differentiating mucinous from non-mucinous cysts and suffer from high interobserver variability, even among experts (1, 2). In a large multicenter study (cooperative pancreatic cyst study) using receiver operating curve analysis, cyst fluid CEA (threshold of 192 ng/mL) demonstrated superior accuracy for the distinction of mucinous from non-mucinous lesions with a sensitivity of

75% and specificity of 84% (8). In the same study, the accuracy of CEA (79%) was significantly greater than the accuracy of EUS morphology (51%) and cytology (59%), and there was no combination of tests that provided greater accuracy than CEA alone (8). The combination of EUS morphology, cytology, and CEA findings was more sensitive than CEA alone (91% vs. 75% respectively) but less specific (31%) (8).

### ***Surgical recommendations and radiologic features of malignant pancreatic cysts***

The current surgical recommendation is resection for suspected IPMN with main duct involvement and MCN in surgically fit patients (1, 7). However, IPMN with branch duct involvement can be observed if (i) the cyst size is less than 3.0 cm; (ii) there is absence of an intramural nodule; (iii) the patient is asymptomatic; (iv) the main pancreatic duct is less than 6 mm wide; and (v) cyst fluid cytology is negative for malignancy (1, 7). The presence of a solid mass or mural nodule in either multilocular or unilocular cysts, main pancreatic duct dilatation > 10 mm, thick septations, and biliary obstruction are characteristic radiologic features of malignancy (3), and imaging may be used as a surveillance tool for longitudinal follow-up of these lesions that could progress to malignancy (3). Radiologic imaging has limited diagnostic accuracy (approximately 40%), as different types of cysts display overlapping features (7), as evidenced by the relatively low sensitivity and specificity of EUS morphology alone (56% and 45%, respectively) (8). In the absence of an associated mass, there are no reliable radiologic features that distinguish benign and premalignant cysts from malignant cysts (9). A large multicenter study found an accuracy of EUS for the diagnosis of mucinous versus non-mucinous cysts of only 51% (4). Several EUS features have been proposed as indicators of increased risk of malignancy, including thick wall, presence of septations, and the presence of intramural nodules and masses (1, 4).

### ***Utility of cytologic evaluation in pancreatic cyst fluid analysis***

Cytology is currently the most widely used test for diagnosing malignancy in pancreatic cysts (10). The cytologic detection of high-grade dysplasia leads to early intervention either surgically or with cyst ablation therapy (10). Cytology is still a more powerful tool for early detection of cancer than other high-risk imaging features,



including the presence of a mural nodule or dilatation of the main pancreatic duct (10). The sensitivity of cytology for diagnosing a mucinous cyst was 35% with a high specificity of 83% (8). The overall accuracy of cytology (59%) was similar to the overall accuracy of EUS morphology (51%); however, EUS imaging was significantly less specific (45%) (8). The sensitivity of cytology for diagnosing malignancy in a malignant mucinous cystic lesion is low however, at 22% (8), and the accuracy of cytology alone in distinguishing between mucinous and non-mucinous cysts ranges widely from 59% to 100% (11). Finally cytology has limited sensitivity for the detection of serous cystic tumors, with a positive result in only 38% of cases (2).

### ***Adjunct utility of biochemical and tumor markers for identifying malignant pancreatic cysts***

There are several biochemical (amylase) and tumor markers [carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9)] that are useful in distinguishing benign pancreatic cysts from malignant pancreatic cysts (12). Currently, the most useful biochemical tumor marker that confirms a mucinous cyst is carcinoembryonic antigen (CEA), with 79% accuracy using a threshold CEA level of 192 ng/mL (8,12). Additionally, CA 19-9 is the most utilized serum-based marker for pancreatic cancer diagnosis, and is currently used for detection of recurrent disease and surveillance of patients following surgery (12).

A recent study demonstrated that both CEA and CA19-9 were significantly elevated in patients with malignant pancreatic cysts as compared to benign lesions (12). The sensitivity for CEA (cut-off, 45 ng/mL) and CA 19-9 (cut-off, 37 U/ml) were 91.8% and 81.3% respectively, while the specificity for CEA and CA 19-9 were 63.9% and 69.4%, respectively (12). The positive predictive value (PPV) of CEA and CA 19-9 were 53.6% and 89.3%, respectively, while the negative predictive value (NPV) for CEA and CA 19-9 were 95.8% and 54.2%, respectively (12). In contrast, amylase levels were significantly higher in benign lesions than malignant pancreatic cysts (12), while the highest levels of amylase are usually observed in pseudocysts (12). However, the sensitivity and specificity (62.5% and 69.4%, respectively) of amylase for diagnosing premalignant and malignant pancreatic cysts was lower than that for CEA and CA 19-9 (12). Furthermore, the PPV and NPV for amylase were also lower (47.6% and 80.6%, respectively) (12). While it has been reported that a higher sensitivity (100%) and specificity (63.6%) could be achieved at a cut-off amylase level of 5,000 U/L for differentiating pseudocysts from all other pancreatic cysts (12), amylase levels > 250 U/l are currently accepted as the threshold for differentiating pseudocysts from mucinous cystic neoplasms (2).

### ***Molecular markers that confirm malignancy in mucinous cysts***

Several molecular markers have been investigated in the hopes of improving the detection of malignant pancreatic cysts using pancreatic fluid analysis (6, 13-18). These include K-ras (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) mutation, DNA quantity and quality, and microsatellite allelic loss amplification (6, 9, 13-18). In one study, the accuracy of DNA concentration, K-ras mutation, and allelic imbalance were reported as 37%, 21%, and 73%, respectively; however, when all modalities of molecular analysis were combined, the overall accuracy increased to 79% (14).

The presence of elevated amounts of pancreatic cyst fluid DNA, high amplitude mutations, and specific mutation acquisition sequences are indicators of malignancy (15). Cyst fluid K-ras mutation was helpful in the diagnosis of mucinous cysts with a high specificity but low sensitivity (sensitivity 45%; specificity 96%) (15). Components of DNA analysis useful in detecting malignant cysts include allelic loss amplitude over 82% (sensitivity 67%; specificity 66%) and high DNA amount (sensitivity 90%; specificity 67%) (15). The presence of an initial high-amplitude K-ras mutation followed by allelic loss was highly specific (96%) for the presence of malignancy in a cyst but suffered low sensitivity (37%) (15).

Typically, molecular analysis of pancreatic cyst fluid can be performed on 200 µL of cyst fluid (2). In some institutions, detection of K-ras mutation is the only currently used molecular marker for the diagnosis of IPMN and MCN (2), is easily performed in many laboratories and requires only minute amounts of material (less than 1mL) for cyst fluid analysis (2).

In a recent study that evaluated CEA and molecular analysis (DNA quantity, K-ras mutation and 2 allelic imbalance mutations) for differentiating mucinous from non-mucinous cysts, CEA showed higher sensitivity (82%) compared to molecular analysis (77%) (14). However when both CEA and molecular analysis were combined, the sensitivity reached 100% (14). In another study that evaluated the correlation of DNA mutational analysis of pancreatic cyst fluid with cyst fluid CEA and histologic diagnosis, investigators found agreement amongst histology, CEA levels, K-ras mutation, and LOH mutations (2) was present in only 35% of cases (all were benign cysts), whereas elevated CEA was more predictive of malignant cysts than K-ras or LOH (2) mutations (17). In addition, CEA demonstrated a slightly higher NPV than molecular testing, leading the authors to suggest that K-ras or LOH (2) mutations should be used selectively rather than routinely in the analysis of these specimens (17). Similarly,

another study evaluated the correlation between a commercially available molecular analysis test (K-ras-2 gene point mutation, LOH, and DNA quantity/quality) and clinical consensus diagnosis (EUS features, CEA levels, and cytologic examination) (16). This study showed 83% concordance between molecular and clinical consensus diagnosis (16). The sensitivity, specificity, and PPV of molecular diagnosis were 83%, 100%, and 100% for a malignant cyst, and 86%, 93%, and 95% for a benign mucinous cyst, respectively (16), leading the investigators to conclude that molecular analysis supplements the diagnostic value of pancreatic cyst fluid analysis (16). Other studies have confirmed that molecular analysis significantly increases the diagnostic yield of pancreatic cystic neoplasms when used in conjunction with cytology and cyst fluid CEA levels (6, 13).

Recently, investigators have evaluated microRNAs [miRNAs, small non-coding RNA (17-25 nucleotides)] that regulate gene expression at the post-transcriptional level (2)] using whole-genome expression for distinguishing between benign, premalignant, and malignant pancreatic cysts (19), and found that miRNA-21 is a potentially good candidate biomarker that predicts not only the presence of invasive cancer at the time of evaluation but also of histologic progression and cancer development over time (19). Furthermore, miRNA-22 was found to be useful in the identification of more advanced malignant disease (19). Additional studies of molecular markers has revealed mutation of RNF43, a gene located on chromosome 17q, is present in 75% and 50% of IPMN and MCN cysts, respectively (20). Similarly, a recurrent mutation of alpha stimulating activity polypeptide 1 (GNAS) was identified in 62% of IPMN cysts (20). Lastly, the von-Hippel-Lindau gene (VHL) mutation was commonly identified in serous cystadenoma (20). Such recurrent mutations represent potentially useful biomarkers as we attempt to further refine the diagnosis of cystic lesions of the pancreas.

## References:

1. Khalid A, and Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol* 2007; 102: 2339-2349.
2. Rockacy M, Khalid A. Update on pancreatic cyst fluid analysis. *Ann Gastroenterol* 2012; 26(1): 1-6.
3. Pitman MB, Lewandowski K, Shen J, et al. Pancreatic cysts: preoperative diagnosis and clinical management. *Cancer Cytopathol* 2010; 118:1-13.
4. Bhutani MS, Gupta V, Guha S, Gheonea DI, Sftoiu A. Pancreatic cyst fluid analysis – A review. *J Gastrointestin Liver Dis* 2011; 20(2): 175-180.
5. Sreenarasimhaiah J, Lara LF, Jazrawi SF, Barnett CC, Tang SJ. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. *JOP* 2009; 10(2): 163-8.
6. Toll AD, Kowlaski T, Loren A, Bibbo M. The added value of molecular testing in small pancreatic cysts. *JOP* 2010; 11(6): 582-586.
7. Park WG. Screening for pancreatic cancer: what can cyst fluid analysis tell us? *F1000 Medicine Reports* 2011, 3(3): 1-4.
8. Brugge WR, Lewandowski K, Lee-Lewandowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; 126: 1330-1336.
9. Khalid A, McGrath KM, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. *Clinical Gastroenterology and Hepatology* 2005; 3: 967-973.
10. Pitman MB. Pancreatic cyst fluid triage. *Cancer Cytopathol* 2013; 57-60.
11. Panarelli NC, Sela R, Schreiner AM, et al. Commercial molecular panels are of limited utility in the classification of pancreatic cystic lesions. *Am J Surg Pathol* 2012; 36 (10): 1434-144.
12. Talar-Wojnarowska R, Pazurek M, Durko L, et al. Pancreatic cyst fluid analysis for differential diagnosis between benign and malignant lesions. *Oncology letters* 2013; 5:613-616.
13. Al-Haddad M, DeWitt J, Sherman S, et al Performance characteristics of molecular (DNA) analysis in the diagnosis of mucinous pancreatic cysts. *Gastrointestinal Endoscop* 2014; 79(1): 79-87.
14. Sawhney MS, Devarajan S, O'Farrel P, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; 1106-1110.
15. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PAND study. *Gastrointest Endosc* 2009; 69: 1095-1102.
16. Shen J, Brugge WR, DiMaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid. *Cancer Cytopathol* 2009; 117:217-227.
17. Sreenarasimhaiah J, Lara LF, Jazrawi SF, Barnett CC, Tang SJ. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. *JOP* 2009; 10(2): 163-168.
18. Finkelstein SD, Bibbo M, Loren DE, et al. Molecular analysis of centrifugation supernatant fluid from pancreaticobiliary duct samples can improve cancer detection. *Acta Cytol* 2012; 56: 439-447.
19. Farrell J, Toste P, Wu N, et al. Endoscopically acquired pancreatic cyst fluid MicroRNA 21 and 221 are associated with invasive cancer. *Am J Gastroenterol* 2013; 108: 1352-1359.
20. Wu J, Jiao Y, Molin MD, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci* 2011;108(52):21188-93.

# Case Report

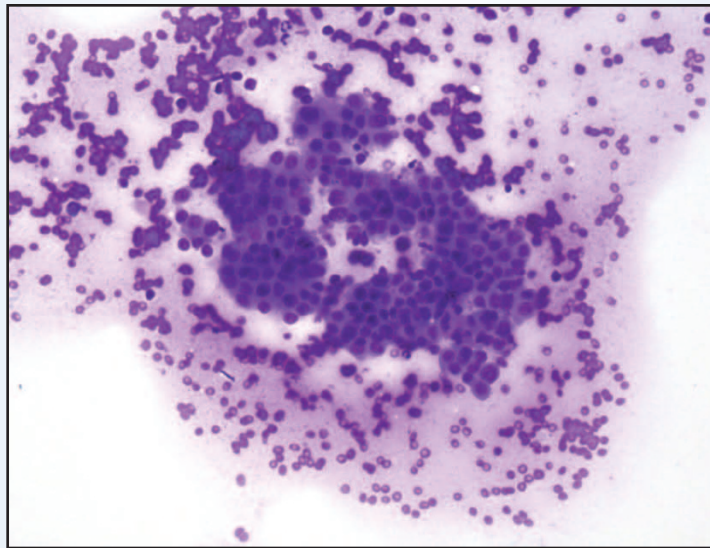


## Ricardo R. Lastra, MD

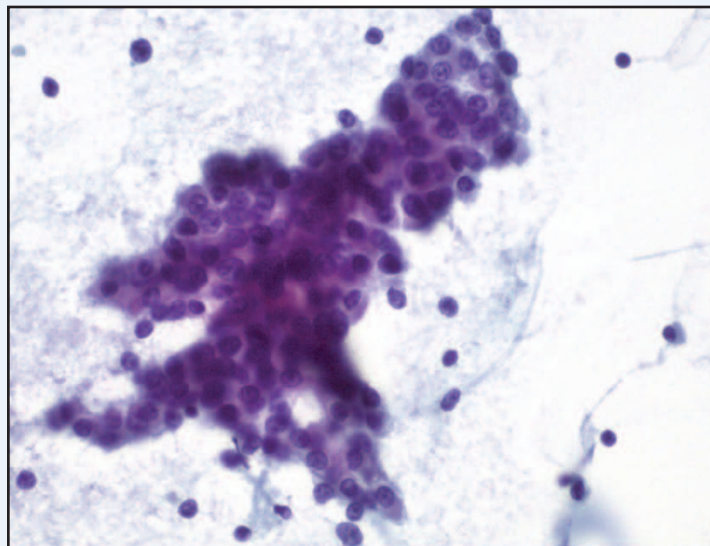
Department of Pathology and Laboratory Medicine,  
Hospital of the University of Pennsylvania, Philadelphia, PA

### Clinical History

61 year old male patient with a long standing history of hepatitis C, presented with left shoulder pain which started a few months prior to presentation, after being involved in a motor vehicle accident. The pain irradiated to the left arm and was associated with loss of strength. Review of symptoms revealed an unintended weight loss of 125 lbs, which started 1 year prior to presentation, and worsening dyspnea. MRI of the left shoulder was performed, which showed a large expansile lytic mass arising from the left scapula, with an associated 9.7 x 3.8 cm soft tissue mass. Additional imaging revealed multiple liver nodules in a background of cirrhosis, as well as multiple lung nodules and lytic lesions in various ribs. Ultrasound-guided fine needle aspiration of the left shoulder mass and liver lesions were performed. The findings were similar in both specimens. Representative images from the FNA of the shoulder mass are shown in Figures 1-4.



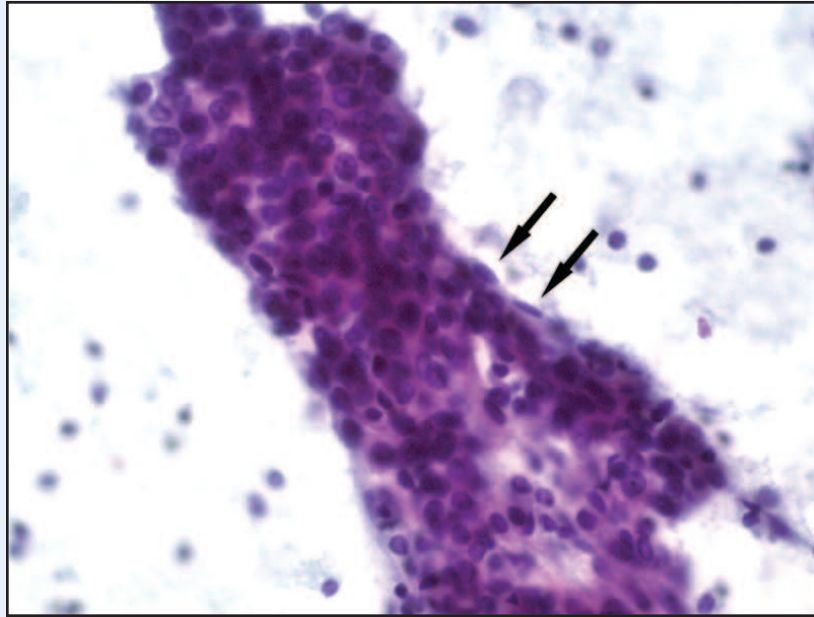
**Figure 1.** Left shoulder mass FNA smear. Diff-Quik stain, 20x.



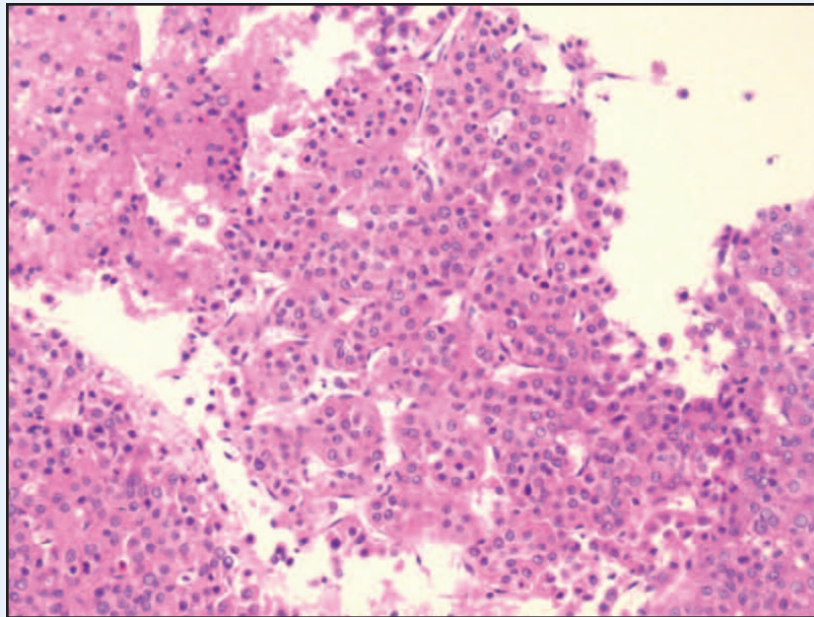
**Figure 2.** Left shoulder mass FNA smear. Pap stain, 40x.



# Case Report



**Figure 3.** Fragment of tumor cells with lining endothelial cells (arrows). Pap stain, 40x.



**Figure 4.** Cell block material from shoulder mass FNA. H&E stain, 20x.

# Case Report

## Questions

1. According to the clinical scenario and cytologic features, the most likely diagnosis is:
  - a) Metastatic renal cell carcinoma
  - b) Metastatic ductal carcinoma of breast
  - c) Metastatic hepatocellular carcinoma
  - d) Sarcoma
  - e) Sebaceous carcinoma
2. Which of the following are characteristic cytomorphologic features of this entity:
  - a) Cohesive cell clusters in acinar, pseudoglandular or trabecular arrangements
  - b) Peripheral endothelial cells lining the cell fragments
  - c) Binucleation and intranuclear cytoplasmic inclusions
  - d) Atypical bare nuclei in background
  - e) All of the above
3. Which of the following staining patterns is most consistent with the morphologic impression:
  - a) Cam 5.2 (+), AE1/3 (+), pCEA (-) and AFP (+)
  - b) Cam 5.2 (+), AE1/3 (-), pCEA (+) and AFP (+)
  - c) Cam 5.2 (+), AE1/3 (+), mCEA (+) and AFP (+)
  - d) Cam 5.2 (+), AE1/3 (-), mCEA (+) and AFP (-)
  - e) Cam 5.2 (+), AE1/3 (+), pCEA (+) and AFP (+)
4. Which of the following is the most significant risk factor for the development of this neoplasm worldwide:
  - a) Hepatitis B
  - b) Hemochromatosis
  - c) Primary biliary cirrhosis
  - d) Hepatitis C
  - e) Alcoholic cirrhosis

## Answers

1. C

2. E

3. B

4. A

## Discussion

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, although its incidence shows striking variations according to geographic location (much more common in East Asia and Sub-Saharan Africa, and less common, but on the increase, in the United States and Europe).<sup>1</sup> It is a complex disease with many risk factors, and is preceded by cirrhosis in the majority of cases; hence, causes of cirrhosis have been identified as risk factors of HCC.<sup>1</sup> Hepatitis C virus (HCV) infection is associated with the highest incidence of HCC in patients with cirrhosis in North America, while hepatitis B virus (HBV) infection and exposure to aflatoxin B1 are the dominant risk factors in East Asia and Africa.<sup>2,3</sup> Hemochromatosis, alcoholic cirrhosis and primary biliary cirrhosis have also been identified as risk factors for development of HCC.<sup>2</sup>

Early detection and treatment of HCC is the sole option for achieving long term survival. Since patients may remain asymptomatic until decompensation of the cirrhosis leads to imaging studies and the finding of a liver mass, surveillance with ultrasonography and serum  $\alpha$ -fetoprotein (AFP) is necessary to reduce disease-related mortality.<sup>3</sup> Unfortunately, it is not uncommon for metastatic disease to be the primary presentation of HCC, and it is estimated that 40-85% of the cases have secondary lesions at the time of primary diagnosis.<sup>4</sup>

Metastasis of HCC is often via a hematogenous route, and the most common sites of metastatic disease are the lungs and lymph nodes. Soft tissue dissemination is exceptionally rare; Terada et al. reported a single case of shoulder soft tissue metastasis in a review of 31 autopsy cases in patients with HCC.<sup>5</sup> In general, metastatic HCC to soft tissue is limited to isolated case reports, including facial subcutaneous tissue, gluteal and sacral regions, scapular area and scalp.<sup>6-9</sup> Although bone is also considered a relatively common site for HCC metastasis, the presence of a large, destructive lytic lesion with a major soft tissue component is uncommon.

It is not uncommon for the primary diagnosis of HCC to be performed via fine needle aspiration (FNA), either of a liver mass or of a metastatic deposit. Fine needle aspiration biopsies characteristically yield a highly cellular specimen composed of cohesive clusters of cells in an acinar, pseudoglandular or trabecular arrangement, with abundant stripped but atypical nuclei in the background. The tumor cells show abundant granular and eosinophilic cytoplasm, occasionally with bile pigment. Fine vacuolation of the cytoplasm is often present. The nuclei are most commonly rounded, with vesicular chromatin and a prominent, centrally located, eosinophilic nucleolus. The presence of binucleation and intranuclear cytoplasmic inclusions is commonly seen. When dealing with FNA specimens from a metastatic site in a patient without a previous diagnosis of HCC, the presence of capillaries transgressing fragments of tumor cells and the peripheral lining of these cellular fragments by endothelial cells are both excellent diagnostic clues that should raise the suspicion of metastatic HCC. Frank pleomorphism, mitosis and necrosis may be observed in cases of poorly differentiated HCC.

Fine needle aspiration specimens of well-differentiated HCC located in the liver can very closely resemble normal liver parenchyma, and this distinction can be problematic. In fact, a "negative" FNA biopsy of a liver lesion in a patient with cirrhosis may not rule out the presence of HCC, as the false negative rate can be as high as 30% due to the absence of specific histologic hallmarks for its diagnosis.<sup>10</sup> Subtle morphologic clues, such as the lack of ductal epithelial elements, and clinical and radiologic correlation may be helpful in achieving a diagnosis of malignancy. Conversely, a diagnosis of well-differentiated HCC can be relatively straightforward in a metastatic site, but in cases of metastatic poorly differentiated HCC, the diagnosis may not be possible by cytomorphology alone, and the use of ancillary techniques (such as immunohistochemistry) may be necessary. Characteristically, HCC is positive for Cam 5.2 and negative for AE1/3. Positive staining for alpha fetoprotein (AFP) is considered quite specific for HCC, but its sensitivity is low.<sup>11</sup> Polyclonal CEA antibodies typically show a canalicular staining pattern as a result of cross-reactivity with biliary glycoprotein I, but monoclonal CEA is usually negative.<sup>11,12</sup> Hepatocyte paraffin 1 (Hep-Par1) has been described as a reliable marker for HCC, particularly in poorly differentiated cases, showing a high sensitivity and specificity for hepatocellular carcinomas.<sup>13</sup> Other stains that have been reported as useful in the diagnosis of HCC include CD10 (canalicular pattern similar to that seen in pCEA), CK8 and CK18.<sup>14</sup> CD34, found in normal endothelium but absent in normal sinusoids, can highlight regions of sinusoidal capillarization, where the sinusoids have acquired characteristics of capillary endothelial cells.<sup>14</sup>

When dealing with an FNA specimen of a mass (from the liver or elsewhere) in a patient with history of cirrhosis, the possibility of HCC must always be considered. This is true even when this possibility is not considered on the basis of clinical presentation, as demonstrated by this case. Once the possibility of HCC arises, the combination of cytomorphologic features and immunohistochemical stain results is generally sufficient to make a definitive diagnosis.

## References

1. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: A global and regional perspective. *Oncologist*. 2010;15 Suppl 4:5-13.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. *Gastroenterology*. 2004;127(5 Suppl 1):S35-50.
3. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379(9822):1245-1255.
4. Auclin E, Camilleri C, Dubreuil O, et al. An unusual recurrence site for HCC! *Clin Res Hepatol Gastroenterol*. 2013;37(1):e29-31.
5. Terada T, Maruo H. Unusual extrahepatic metastatic sites from hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2013;6(5):816-820.
6. Gilsanz Fernandez C, Garcia Castano J, Garcia Roman M, Rodriguez Dorrego R, Cabrero Gomez F, Lopez de la Riva M. A gluteal mass as the initial manifestation of a calcified hepatocarcinoma. *Rev Esp Enferm Apar Dig*. 1989;76(2):181-184.
7. Nava VE, Liu ML. Hepatocellular carcinoma metastases to facial subcutaneous tissue. *Arch Pathol Lab Med*. 2010;134(6):809-2165-134.6.809.a.
8. Rastogi A, Bihari C, Jain D, Gupta NL, Sarin SK. Hepatocellular carcinoma presenting with multiple bone and soft tissue metastases and atypical cytomorphological features--a rare case report. *Diagn Cytopathol*. 2013;41(7):640-643.
9. Young C PM. Hepatocellular carcinoma presenting as musculoskeletal metastasis: A report of two cases. . April 2007;62(1):25-29.
10. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology*. 2008;47(1):97-104.
11. Hurlimann J, Gardiol D. Immunohistochemistry in the differential diagnosis of liver carcinomas. *Am J Surg Pathol*. 1991;15(3):280-288.
12. Loo KT, Tsui WM, Chung KH, Ho LC, Tang SK, Tse CH. Hepatocellular carcinoma metastasizing to the brain and orbit: Report of three cases. *Pathology*. 1994;26(2):119-122.
13. Wennerberg AE, Nalesnik MA, Coleman WB. Hepatocyte paraffin 1: A monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. *Am J Pathol*. 1993;143(4):1050-1054.
14. Wee A. Diagnostic utility of immunohistochemistry in hepatocellular carcinoma, its variants and their mimics. *Appl Immunohistochem Mol Morphol*. 2006;14(3):266-272.

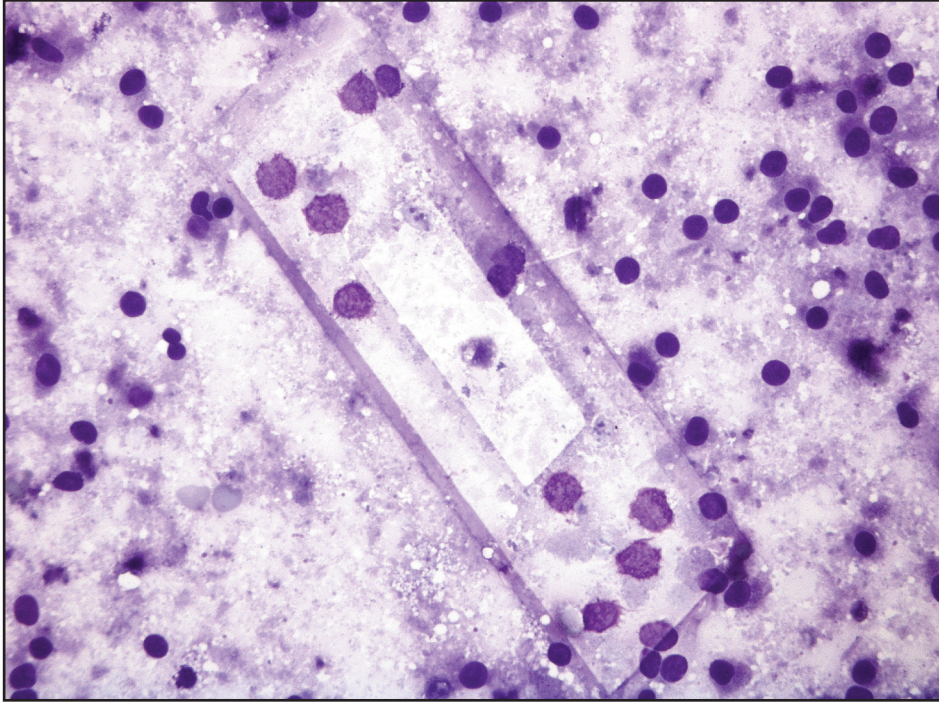
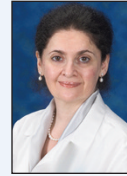


# Images in Cytology

## IMAGES IN CYTOLOGY

**T. Giorgadze, MD, PhD**

Department of Pathology and Laboratory Medicine  
New York-Presbyterian Hospital/Weill Cornell Medical College  
New York, NY

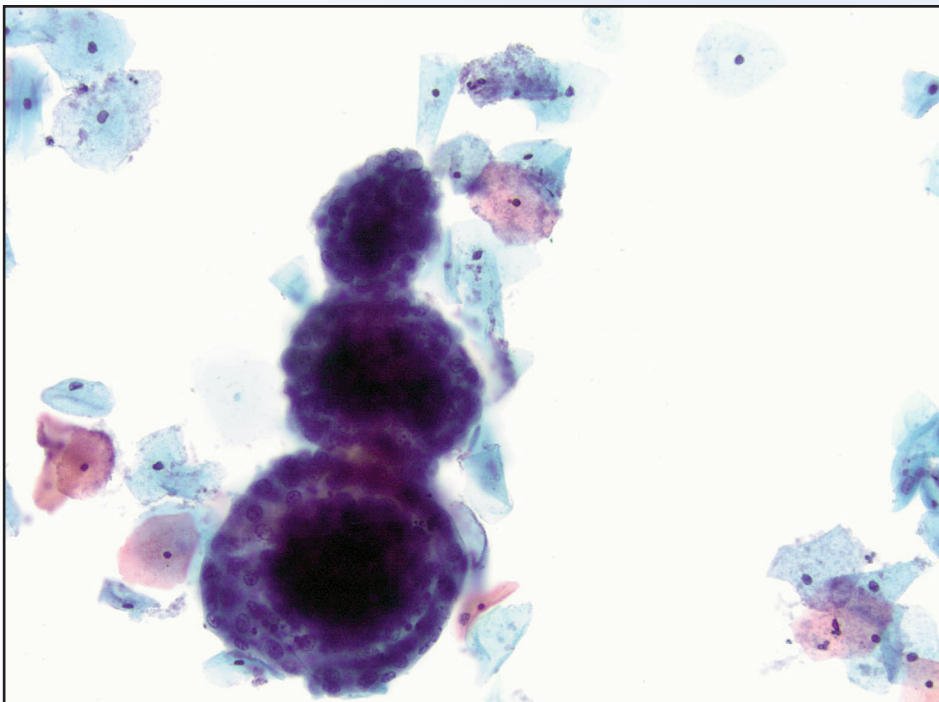


### The Doorway

Among many diagnostic advantages of air-dried cytologic preparations stained by Romanowsky-type stain is better visualization of intercellular material <sup>(1)</sup>. In this Diff-Quik stained aspirate from solid-pseudopapillary tumor of the pancreas the presence of a striking negatively stained phantom image of cholesterol crystal opened the door to recognition of longstanding cystic component. This low malignant potential neoplasm commonly shows degenerative changes and presents as cystic pancreatic tumor <sup>(2)</sup>.

### References:

1. Krafts KP, Pambuccian SE. Romanowsky staining in cytopathology: history, advantages and limitations. *Biotechnic & Histochemistry*. 2011; 86(2): 82-93
2. Klimstra DS, Wenig BM, Hefes CS. Solid-pseudopapillary tumor of the pancreas; a typically cystic carcinoma of low malignant potential. *Semin Diagn Pathol*. 2000 Feb; 17(1): 68-80



### The Marching Cells

These marching benign appearing endometrial cells are of no clinical significance and can safely pass across Pap smear border check.





Dedicated to Clinical Practice - Clinical Education - Clinical Research  
George N. Papanicolaou  
1883-1962

## JOIN THE PSC!

### **NEW Benefits to PSC members:**

**Special annual subscription rate of \$60  
to the journal "Cancer Cytopathology"**

*Will include the print journal (12 issues in 2014)  
as well as electronic access*

*Effective with Volume 122/Publishing year 2014*

**Discount \$50 subscription rate for paper  
copy of "CytoJournal" (vs. regular \$375)**

**The Membership Committee**

**APPLY TODAY:** <http://www.papsociety.org/members.html>

# PSC Membership - Apply Today!

Membership..

<http://www.papsociety.org/members.html>



MEMBERS ONLY

Download Membership Directory

Lost Username or Password?

## Benefits to PSC members

- Focus Newsletter
- Diagnostic Cytopathology subscription  
(may donate the copy to pathologist in underserved country)
- 'CytoJ OA Stewards- Plus' benefits :-
  - Waiver of \$1500 Article Publication Charge,
  - FREE PDF of all CytoJournal articles,
  - Optional print copy of CytoJournal at nominal annual subscription,
  - & many other benefits <http://www.cytojournal.com/OASteward.asp>
- Representation at the USCAP
- Representation at the European Congress of Cytopathology
- E-learning education initiatives
- Image atlas access
- Membership directory

Papanicolaou Society of Cytopathology (PSC) is  
'CytoJournal OA Stewards'



**CYTOJOURNAL**  
[www.cytojournal.com](http://www.cytojournal.com)



Peer-reviewed, Open access, Pub-Med indexed  
Scholarly Cytopathology Journal

All PSC members entertain 'CytoJ OA Stewards' benefits  
(for details visit <http://www.cytojournal.com/OASteward.asp>).

all materials to:

Dedicated to Clinical Practice ☐ Clinical Education ☐ Clinical Research  
George N. Papanicolaou  
1889-1962  
By whose letterhead it be known that

Join today by downloading and filling the  
membership form from  
<http://www.papsociety.org/docs/09/pscapp2009.pdf>

NAME

is a member of the Papanicolaou Society of Cytopathology  
YEAR

You will be emailed a certificate as shown here

Martha Bishop Pitman, M.D.  
President, PSC

(Please forward this to your colleagues)

Eric Suba, M.D.  
Treasurer, PSC