

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 Oluwale Fadare, MD as guest editor for December 2011 issue of Focus. I thank Dr. Fadare for the excellent organization and appreciate the hard work.

Please enjoy the issue and Happy Holidays to all PSC members.

Sincerely,

Vinod B. Shidham,
MD, FRCPATH, FIAC

Presidential Message for Focus



The future for cytology presents many new opportunities for cytopathologists to contribute to patient care. The Papanicolaou Society as a pathologist-based educational society plays an important role in preparing cytopathologists to contribute in new ways to diagnostic medicine including personalized medicine. The Society is presenting a series of cutting edge educational programs both within the United States and internationally. These presentations include scientific programs at the USCAP in association with the ASC. The Papanicolaou Society has presented a number of educational programs at the European Congress of Cytology most recently at Istanbul. Several members of the Papanicolaou Society will contribute to the program at the IAP meeting in South Africa. In addition to these

Con't on page 3

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IN THIS ISSUE

From Editor's Desk	1
President's Message	1
Humanities Corner	2
On the "Pawnball megakaryocyte"	
Timely Topics	12
Viewpoint: Cytology-Based	
Screening in India	14
Cytology and HIV	
News & Announcements	17
Membership Info	20

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From the Guest Editor's Desk



Oluwale Fadare, MD

This issue of Focus features an interesting, albeit eclectic amalgam of the conventional and unconventional, the educational and the entertaining. The Presidential message updates the PSC membership and the general readership on the myriad activities of the Society, all of which are ultimately geared towards improved patient care. In The Humanities corner, Dr Manon Auger provides an insightful and sprawling review of the book "The emperor of all maladies-a biography of cancer", which should be of interest to all readers. In the spirit of the season, Drs Rajan Dewar and David Steensma contribute a "tongue-in-cheek" look at a Cytology-Christmas connection, centered on the "Pawn ball

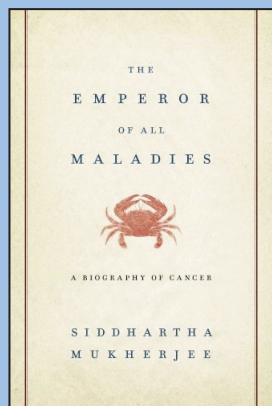
Con't on page 3

The Humanities Corner

About "The emperor of all maladies-a biography of cancer"- a recommended reading

(Part I)

by: Manon Auger, MD, FRCP(C)
McGill University Health Center and McGill University



To say that the book "The emperor of all maladies- a biography of cancer" is a book I recommend is an understatement; in fact, this is a "must-read" for anyone directly or indirectly involved with medicine; it is, a page-turner, a thriller of the history of cancer. Instead of the expected interesting but dry chronological account of the field of cancer and oncology, this book is written in such a personal style that it made me go through a roller coaster of emotions ranging from awe to surprise, and which many times, brought tears to

my eyes. This is the best book, all categories confounded, that I have read in a very long time.

The author, Siddhartha Mukherjee, a former Rhodes scholar, is a young oncologist and researcher at Columbia University and Columbia University Medical Center. He decided to write this book in response to the question posed by a patient who was confronting a relapse from an aggressive form of abdominal cancer: "I'm willing to go on, but I need to know what it is I'm battling". The book is Mukherjee's attempt to answer her question by going back to the origin of the disease and tracing its development through history. An important message that the author very successfully conveys in his book, is that there are many patients who gave up their lives, especially in the early years of oncology, to help scientists understand cancer. Indeed, Mukherjee skillfully shares, in a very respectful manner, personal details of the stories of these patients and of their families during the early babblings of oncology. He also brilliantly describes numerous behind-the-scenes details and anecdotes of the big names of the cancer field, names for many of us familiar but oft times abstract, such as Farber, Halsted, Kaplan, Hodgkin, and brings them all to life in this wonderful book.

I cannot give real justice to this book by highlighting some interesting facts mentioned in it; you really have to read the book yourself. However, I just cannot resist sharing some of those with you. What follows is the first installment of highlights of this book; others will follow in subsequent editions of Focus.

• About "cancer" and "oncology"

It was Hippocrates, who, around 400 BC, coined a term for cancer in the medical literature: "karkinos", from the Greek word for "crab". The tumor, surrounded by prominent blood vessels, reminded him of a crab in the sand with its legs spread in a circle. Later the analogy with a crab was also made because cancer can produce a sudden stab of pain just like being caught in the grip of a crab's pincers.

"Onkos" was also a Greek word occasionally used to describe tumors, a term from which "oncology" is derived from.

Onkos was the Greek term for a mass, load or burden; cancer was viewed as a burden carried by the body.

• About Virchow

When Virchow entered the world of medicine in the early 1840s, the causes of disease were attributed to invisible forces such as neuroses, hysterias and bad humors. He revolutionized this world by examining cells under the microscope. Here are some of his achievements:

In 1845, Rudolf Virchow, then only a 24 year-old German researcher, published a case report in which he described a condition that he initially named "weisses Blut", or "white blood" because of the millions of white blood cells he had seen under the microscope. In 1847, he changed the name to "leukemia", derived from 'leukos', the Greek word for "white".

Extending the claim made in 1838 by Matthias Schleiden, a botanist, and by Theodor Schwann, a physiologist, that all living organisms were built from fundamental building blocks called cells, Virchow stated that human bodies (like the bodies of animals and plants) were composed of cells. He also stated that cells only arose from other cells-*omnis cellula e cellula*.

He deduced that if cells arise only from cells, then growth could only occur by either by increasing cell numbers (i.e. hyperplasia) or by increasing cell size (i.e. hypertrophy). From normal tissue, he extrapolated to the abnormal, new growths, i.e. neoplasia, as he coined them. By 1902, when he died, a new theory of cancer had emerged out of his observations: cancer was now considered a disease of pathological hyperplasia in which cells acquired an autonomous will to divide.

• About Sidney Farber

A common thread through a large part of the book relates to Sidney Farber. Sidney Farber was a pediatric pathologist whose office was in the basement (where else!) of the Boston Children's Hospital, and who, by the mid-1930s, was recognized as an eminent pathologist who had written a textbook, *The Postmortem Examination*, considered a classic in the field. By 1947, however, Farber had become listless of taking care of the dead rather than the living and had decided that he needed to make a drastic professional change: he was going to channel his energy into using his knowledge of pathology to develop new therapeutic interventions.

He chose to focus on acute lymphoblastic leukemia (ALL), which was then universally lethal, because he was looking for a disease on which the impact of therapy could be easily quantified by objective means: ALL satisfied that criterion because the leukemia cell count could easily be monitored by looking at a blood or bone marrow sample under the microscope.

Extrapolating from the observations that folic acid, if administered to nutrient-deprived patients, could restore the

normal genesis of blood, Farber wondered whether giving folic acid to leukemic children might also restore normalcy to their blood. This turned out to be a terrible mistake, as folic acid, instead of stopping the leukemia, accelerated it and many children probably died faster with that treatment. With this early trial, Farber attracted the wrath of pediatricians at the Boston Children's Hospital; however, he was intrigued by the phenomenon. He had already started to wonder how an antifolate agent might affect the growth of leukemic cells, and in 1947, he obtained an antifolate, and administered it to a patient, without effect. However, trying a second antifolate, a new drug called aminopterin, Farber started a revolution in the field of oncology: for the first time in the history of leukemia, there was a marked clinical response, a remission. This set

Farber into a flurry of activity and he started to treat more children with ALL. The remissions were short-lasting, but his efforts set ablaze the entire field of chemotherapy. And remember, it was all started by a pathologist...

• Quotes

"A model is a lie that helps you see the truth: - Howard Skipper on the early days of using mice models to test the effects of chemotherapy

"If we didn't kill the tumor, we killed the patient".
-William Moloney on the early days of chemotherapy

Have I piqued your curiosity? If so, do not hesitate a second to read "The emperor of all maladies", for you surely will not regret it.

Reference

1. Mukherjee S. The emperor of all maladies-a biography of cancer. Scribner, New York, 2010, 573p.

Con't from page 1

From the Guest Editors Desk

megakaryocyte". In our Timely topics section, we highlight an article from Dr Walid Khalbuss and colleagues, recently published in Cytojournal, on the cytomorphologic spectrum of neuroendocrine carcinomas in body cavity effusions. As the authors note, these neoplasms present with body cavity effusions at a high frequency. Drs Pam Michelow and Liron Pantanowitz provide a concise and focused update on the role of cytology in the management of the HIV-infected patient, and briefly review new developments in this area. Dr Dhiraj Nikumbh and colleagues provide their personal perspectives on cultural aspects of, and technical limitations to, the effectiveness of cytopathology-based cervical cancer screening programs in some parts of India. Also included in this issue are biosketches of the candidates for the vacant PSC officer positions, a notice for membership renewal, and flyer for the PSC program at the upcoming meeting of the United States and Canadian Academy of Pathologists (USCAP) in Vancouver. Details about the various benefits of PSC membership are highlighted on the last page. We encourage you to be ambassadors of, and advocates for the Society, and to recommend that your colleagues join it. The membership form can be downloaded at www.papsociety.org/docs/09/pscapp2009.pdf. Members and other readers are encouraged to send articles or other contributions (for example, interesting images in cytology, book reviews, case reports, reviews, etc.) to the editor, Dr Vinod Shidham, or any of the Focus editorial board members for consideration.

Finally, I will like to thank Dr Shidham, as well as all the editorial members, for their efforts in putting together this edition of Focus.

Sincerely,
Oluwole Fadare, MD
Guest Editor

Con't from page 1

President's Message

scientific programs and societal meetings, the Papanicolaou Society presents educational material on its website in the form of case presentations. Focus is a valuable mechanism for keeping members of the Papanicolaou Society in touch with societal issues and represents an educational resource which discusses topics of importance to the general cytologic community. The Papanicolaou Society is establishing a Facebook page to aid in communication between members and other individuals.

In conjunction with the ASC, ASCP, American Pancreatic Association and other societies with an interest in pancreaticobiliary disease, the PSC is developing a set of guidelines/recommendations for the cytologic diagnosis of pancreaticobiliary lesions. The results of this effort will be presented at the USCAP Scientific Session in 2013. A website (<http://papsociety.org/pscoforum/>) has been established to solicit broad input for the development of these guidelines. I encourage all interested individuals to view the website and proffer their opinions concerning the cytologic diagnosis of pancreaticobiliary lesions.

As part of the PSCs educational mission, the Society is publishing (Cambridge University Press) a series of monographs on cytologic diagnosis. The first of these is, "Cytohistology: Essentials and Basic Concepts" by Prabodh Gupta, MD and Zubair Baloch, MD. This book covers

general principles in cytology. Other issues to follow include texts on musculoskeletal, liver, head and neck, pulmonary and pancreatic cytopathology. These monographs are written by recognized experts in their fields and contain up to date information for cytopathologists, cytotechnologists and general pathologists.

As part of the PSCs educational mission, the Society is involved in teaching programs in Africa and Southeast Asia. These programs depend on the generosity of individual PSC members including Andrew Field, MD, Eric Suba, MD, Britt-Marie Ljung, MD and others. These individuals donate their time and expertise to give tutorials in Africa and Southeast Asia. The tutorials are well attended and greatly appreciated by the participants.

The Papanicolaou Society carries out other philanthropic activities which help in the continuing education of pathologists and cytotechnologists in Africa and elsewhere. A new initiative by the PSC in conjunction with Wiley-Blackwell involves sending copies of Diagnostic Cytopathology to university and large teaching hospitals in Africa.

The Papanicolaou Society remains a vibrant educational society which invites all of its members to take part in its educational programs both via web-based formats and by the Society's contributions to scientific programs both within the United States and abroad.

Santa Claus, hematopathologist - Cytology of the 'Pawn Ball' megakaryocyte

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It is Christmas and young children await the generous gifts of Santa Claus, who drops (himself and the goods) down the chimney. Santa Claus is also connected to the world of pathology (and hematopathology), through the megakaryocyte.

Figure 1 shows the cytological features of a dysplastic megakaryocyte, termed as the 'pawn ball megakaryocyte' by hematopathologists. What is a 'pawn ball megakaryocyte'? Megakaryocytic nuclear lobes are individual nuclei connected with one another. In addition, even though counting megakaryocytic nuclear lobes is difficult practically, normal megakaryocytic nuclei are always in even number. This is because, nuclear division in megakaryocytes is through a process called 'endo-mitosis', where the nuclei divide in perfect synchrony, resulting in even number of lobes (4 to 128 nuclear lobes!).

A pawn ball megakaryocyte, on the other hand, has two pathognomonic abnormalities: The nuclear lobes are disconnected from each other. In addition, there are odd numbers of nuclear lobes (always three, in order to qualify for the term "pawn ball" megakaryocyte). What is a 'pawn ball'?

Pawn ball is a symbol of pawn broking. Pawn broking has been around several centuries. The pawn broking trade involves exchanging goods, in return for money or other goods. The traditional symbol for pawn brokers is the 'three balls' connected through a small strand. The balls are supposed to represent 'Buy', 'Sell' or 'trade', three essential features of pawn broking. Figure 2 is a picture of the pawn ball symbol outside a pawnshop in Arizona (courtesy, Brad Bryan, Bend, OR).

What is the connection between pawn balls and Saint Nicholas? Let us review the life history of dear old Santa Claus. Santa Claus was born in Myra, in modern day Turkey. In most images, he wears a coat of arm, which portrays the three balls identical to the 'pawn balls'. Saint Nicholas attained his sainthood by giving life to three little infants, who were beheaded and stored in brine (figure 3). The picture of Saint Nicholas blessing the three heads or the children can be seen in many Saint Nicholas shrines throughout the world. In addition, according to another legend, Saint Nicholas is also associated with dropping three bags of gold through a high window (or chimney) that will help as a 'dowry', to get three daughters of a poor man, married. In some of the pictorial representations, the coat of arms carries three bags of gold, and in some images resembles three spherical balls. (A picture of Saint Nicholas Cathedral in Newcastle upon Tyne is shown in figure 4).

Incidentally, an abnormal megakaryocyte which lacks three disjointed nuclei, but falls short to 2 disjointed nuclei is called a Marty Feldman megakaryocyte, named after the actor (young Frankenstein).

Thus, we have a couple of celebrities associated with hematopathology – Santa Claus & Marty Feldman!

Reference:

1. "Pawn ball mega-karyocytes": From the marvelous medici and dear old saint nick to the unsanctified marrow of myelodysplasia. *David P. Steensma*. Hematology, 2003;**8**:11-18.





Research Article

The cytomorphologic spectrum of small-cell carcinoma and large-cell neuroendocrine carcinoma in body cavity effusions: A study of 68 cases

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Abstract

Background: Small-cell carcinoma (SCC) and large-cell neuroendocrine carcinoma (LCNEC) are uncommon in serous body cavity effusions. The purpose of this study is to examine the cytomorphological spectrum of SCC and LCNEC in body cavity serous fluids. **Materials and Methods:** We have 68 cases from 53 patients who had metastatic SCC or LCNEC diagnoses. All cytology slides and the available clinical data, histological follow-up, and ancillary studies were reviewed. **Results:** A total of 68 cases (60 pleural, 5 peritoneal, and 3 pericardial effusions) from 53 patients with an average age of 73 years (age range 43–92 years) were reported as diagnostic or suspicious of SCC (52 cases) or LCNEC (16 cases). The primary site was lung in 56 cases, pancreas in 6 cases, and 2 cases each from cervix, colon, and the head and neck region. Of the 68 cases, 48 cases had no history of malignancy of the same type. Ancillary studies were used in 46 cases (68%) including flow cytometric studies in 5 cases. There were three predominant cytomorphological patterns observed including small-cell clusters with prominent nuclear molding (33 cases, 49%), large-cell clusters mimicking non-small-cell carcinoma (18 cases, 26%), and single-cell pattern mimicking lymphoma (17 cases, 25%). Significant apoptosis was seen in 22 cases (33%) and marked tumor cell cannibalism was seen in 11 cases (16%). Nucleoli were prominent in 16 cases (24%). The most frequent neuroendocrine markers performed were synaptophysin and chromogranin. **Conclusions:** The most common cytomorphologic patterns seen in body cavity effusions of SCC and LCNEC were small-cell clusters with nuclear molding. However, in 51% of the cases either a predominant single-cell pattern mimicking lymphoma or large-cell clusters mimicking non-small carcinoma were noted. In our experience, effusions were the first manifestation of disease in the majority of patients diagnosed with neuroendocrine carcinoma. Therefore, familiarity with the cytomorphological spectrum of neuroendocrine carcinomas in fluid cytology may help in rapidly establishing an accurate diagnosis and in directing appropriate management.

Key words: Cytology, effusion, neuroendocrine carcinoma, small-cell carcinoma

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Khalbuss WE, Yang H, Lian Q, Elhosseiny A, Pantanowitz L, Monaco SE.
The cytomorphologic spectrum of small-cell carcinoma and large-cell neuroendocrine carcinoma in body cavity effusions: A study of 68 cases.

INTRODUCTION

Neuroendocrine carcinomas comprise a heterogeneous group of tumors that represent a spectrum of disease varying from well-differentiated tumors (e.g., carcinoid tumor) to poorly differentiated tumors, such as small-cell carcinoma (SCC) and large-cell neuroendocrine carcinoma (LCNEC). The high-grade or poorly differentiated neuroendocrine carcinomas are characterized by a more aggressive course, early metastases, and poorer prognosis.

SCCs and LCNECs are uncommon in serous body cavity effusions.^[1-3] Due to this rarity, the diagnosis may be challenging for cytopathologists looking at exfoliative cytology specimens. Additional difficulties that may be encountered in fluid cytology include the overlapping morphology between non-neoplastic (lymphocytes) and similar neoplastic entities, scant cellularity, predominance of apoptosis or cellular debris, and artifactual distortion. In addition to the morphological difficulties, there may also be difficulty acquiring sufficient material for ancillary studies.

There are relatively few published reports that discuss the cytomorphologic spectrum of SCCs and LCNECs in serous effusions.^[1-10] The majority of these articles are case reports or only small series of cases.^[1] The goal of this study is to describe the cytomorphological features of SCCs and LCNECs in a large number of serous effusion specimens. In addition, the role of ancillary studies in establishing a diagnosis in difficult cases is discussed.

MATERIALS AND METHODS

During a period of 60 months between January 2005 and December 2009, we examined 5171 serous fluid cytology cases at our institution, of which 53 were identified as positive for SCC and 15 as positive for LCNEC [Tables 1 and 2]. These 68 cases included in this study were identified by retrospectively searching the CoPath computer database for cases that had a diagnosis of small-cell carcinoma or neuroendocrine malignancy in the final diagnosis or diagnostic comment. For each case, data regarding patient age, gender, final diagnosis, diagnostic comments, ancillary studies, previous malignant diagnoses, and all available clinical information and histologic material were recorded. At the time of final interpretation, Papanicolaou-stained, ThinPrep slides, and Diff-Quik-stained cytopsins were reviewed along with two H and E-stained sections from cell block preparations. These slides were evaluated and interpreted in conjunction with the results from ancillary studies to render a final diagnosis. Immunohistochemistry was performed on deparaffinized, formalin-fixed cell block sections using a variety of different antibodies on the Ventana Benchmark® XT system (Ventana Medical Systems, Tucson, AZ), which are listed in Table 3. The following cytomorphological data were gathered from each case: cell

clustering characteristics (small- and large-cell clusters), single-cell arrangements, presence of necrosis/apoptosis, presence of nucleoli, presence of molding, and the presence of tumor cell cannibalism [Table 4]. Each of these parameters was graded as none/rare (<25%), moderate (>25% or more –50%), and significant (>50%). The data were analyzed using descriptive statistics. Institutional review board approval was obtained for this study.

RESULTS

Clinicopathological features

We identified a total of 68 malignant effusions from 53

Table 1: Characteristics of serous effusion cases with SCC and LCNEC (n = 68)

Feature	Total cases	Proportion (%)
Gender: M/F	35/33	1:1
Patient age: average (range), years	73 (43-92)	NA
SCC	53	78
LCNEC	15	22
Cases with lung primary	56	82
SCC	50	
LCNEC	6	
Cases with non-lung primary	12	18
Cases with no history of malignancy	48	71
SCC	44	
LCNEC	4	
Average months of primary to effusion interval (n = 20)	36	
SCC (n = 9)	6.5	
LCNEC (n = 11)	72	
Time interval of primary to metastatic effusion	1-120 months	
Cases with ancillary studies	46	68
Immunostain studies only	41	60
Immunostain studies and flow cytometric studies	5	08

Table 2: Distribution of cases with metastatic serous effusions (n = 68)

Metastatic effusion	Lung	Colon	Pancreas	Cervix	Head/neck
Type of Specimen					
Pleural	52	2	3	1	2
Peritoneal	1	0	3	1	0
Pericardial	3	0	0	0	0
Type of Malignancy					
SCC	50	0	0	2	0
LCNEC	6	2	6	0	2
Total	56 (82%)	2 (3%)	6 (9%)	2 (3%)	2 (3%)

patients with the diagnoses of small-cell carcinoma (53 cases, 78%) and LCNEC (15 cases, 22%). The clinical features of these cases are summarized in Tables 1 and 2. The average patient age was 73 years (range 43–92 years). There were 56 cases (82%) attributed to a lung primary and 12 cases that metastasized from a nonpulmonary primary that included 6 cases from the pancreas, 2 from the colon, 2 from the cervix, and 2 cases from the head and neck region. The location of the effusions was pleural (60 cases), peritoneal (5 cases), and pericardial (3 cases). The majority of the cases had no history of malignancy of the same type (48 cases, 71%), with only 20 cases (29%) having a known diagnosis of SCC or LCNEC at clinical presentation of the effusion.

Cytopathological features

Architecturally, there were three cytomorphological predominant patterns [Figures 1–3 and Tables 4 and 5], including: (1) small-cell clusters with nuclear molding (33 cases, 49%); (2) large-cell clusters mimicking non-

small-cell carcinoma (18 cases, 26%); and (3) single-cell pattern mimicking non-Hodgkin's lymphoma (17 cases, 25%). In both patterns 1 and 2, chains of small cells with nuclear molding were present.

In pattern 1, the cells had a small nuclear size, with a diameter approximately two to three times larger than that of small lymphocytes. The small cells displayed nuclear molding and scant cytoplasm. The nuclei were dark with a finely granular chromatin and inconspicuous nucleoli. In the cell block sections, malignant cells often showed nuclear molding, scant cytoplasm, and a halo around clusters [Figure 1]. In contrast to the background lymphocytes and mesothelial cells, the tumor cells were hyperchromatic, pleomorphic, and displayed marked nuclear contour irregularity. Tumor cell cannibalism was seen in this pattern. This pattern was seen in 69% of LCNEC cases and 42% of SCC cases [Figure 1, middle].

In pattern 2, tumor cells commonly arranged in large clusters mimicking adenocarcinoma. The crescent-shaped

Table 3: Antibodies, clone, host, source, and dilution of antibodies used

Antibody	Clone	Host	Provider	Strength
B72.3/TAG	B72.3	Monoclonal mouse	Biogenex	1:50
BerEP4	Ber-EP4	Monoclonal mouse	Dako	1:20
CA125	OC125	Monoclonal mouse	Ventana	Predilute
Calretinin	n/a	Polyclonal rabbit	Invitrogen	1:100
CD56	123C3.D5	Monoclonal mouse	Cell Marque	Predilute
CD99 - Ewing	12E7	Monoclonal mouse	Dako	1:75
CDX2	CDX2-88	Monoclonal mouse	Biogenex	1:200
Chromogranin	LK2H10	Monoclonal mouse	Ventana	Predilute
Cytokeratin 5/6	D5/16 B4	Monoclonal mouse	Dako	1:50
ER	SP1	Rabbit monoclonal	Ventana	Predilute
KI67	MIB-1	Monoclonal mouse	Dako	1:100
Mammaglobin	304-1A5 and 31A5	Mouse and rabbit mono	Zeta Co.	Predilute
Synaptophysin	n/a	Polyclonal rabbit	Cell Marque	Predilute
TTF-1	8G7G3/1	Monoclonal mouse	Dako	1:50
WT-1	6F-H2	Monoclonal mouse	Dako	1:25

Table 4: Cytomorphologic characteristics of malignant effusions with SCC and LCNEC

Morphologic feature	SCC (n = 53)			LCNEC (n = 15)		
	None/rare %	Moderate %	Significant %	None/rare %	Moderate %	Significant %
Small-cell clusters	3 (6)	28 (53)	22 (41)	1 (7)	3 (20)	11 (73)
Large-cell clusters	28 (53)	7 (13)	18 (34)	8 (53)	7 (47)	0 (0)
Single cells	3 (6)	38 (71)	12 (23)	2 (13)	8 (53)	5 (34)
Apoptosis	31 (58)	10 (19)	12 (23)	0 (0)	5 (33)	10 (67)
Cannibalism	42 (79)	2 (4)	9 (17)	13 (87)	0 (0)	2 (13)
Nucleoli	45 (85)	5 (9)	3 (6)	1 (7)	1 (7)	13 (86)
Nuclear molding	4 (8)	10 (19)	39 (73)	12 (80)	1 (7)	2 (13)

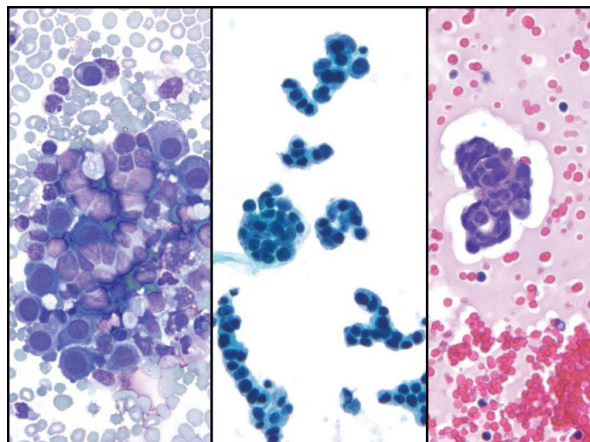


Figure 1: Small-cell carcinoma with a predominance of small clustering and nuclear molding in pleural fluid. The cells of small clusters display nuclear molding and scant cytoplasm (left, DQ, ×400). The nuclei are dark with a finely granular chromatin texture and inconspicuous nucleoli. Cannibalism and some cytoplasm are also seen in middle (Pap Stain, ×200). The cell block (right, H and E stain, ×400) shows a halo around a small cluster, a feature more commonly seen in fluids with adenocarcinoma

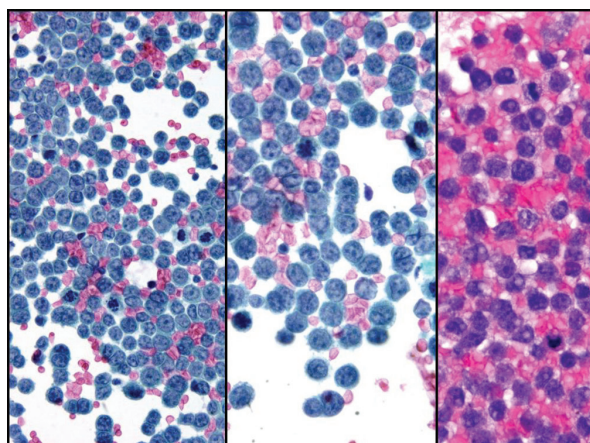


Figure 3: Small-cell carcinoma with a predominant single-cell pattern mimicking lymphoma in pleural fluid. The nuclei show a finely distributed granular chromatin texture and small nucleoli, left and middle (Pap stain, left ×200 and middle ×400). Chains of small cells with nuclear molding (middle, center of the image) and karyorrhexis (left) are seen. In cell block sections (right, H and E stain, ×400) tumor cells display a discohesive pattern

small cells wrapped themselves around one another (onion-ring-like morphology). Chains of small cells with nuclear molding were often present peripheral to the large clusters. In the cell block sections, malignant cells often showed an empty space (lacuna) around large clusters. Large structures showed necrosis in the center mimicking a lumen seen in adenocarcinoma [Figure 2, right]. This pattern was not seen in any of the LCNEC cases but was observed in 35% of SCC cases.

In pattern 3, there was a predominant single-cell pattern that mimicked non-Hodgkin's lymphoma in serous fluids. Chains of small tumor cells with nuclear molding were occasionally seen. The nuclear features of these tumor cells were similar to those noted in pattern 1, such as granular chromatin and inconspicuous nucleoli. Karyorrhexis

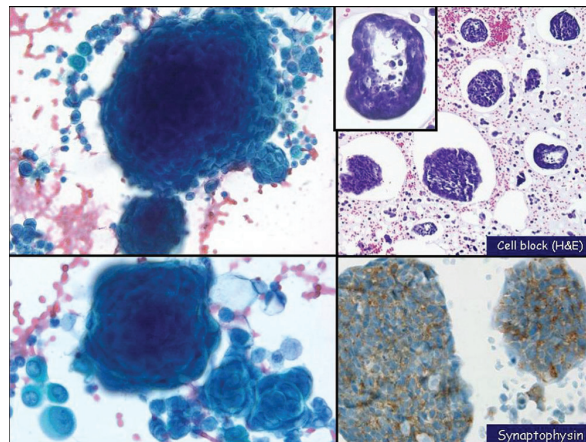


Figure 2: Small-cell carcinoma with a predominance of large clusters in pleural fluid. The cells have wrapped themselves around one another forming large cell clusters (left, Pap stain, ×400). Cell block (right, H and E, ×200) shows a lacuna around large clusters with hollow cores and pseudo-lumen caused by tumor cell necrosis. Synaptophysin immunostain (right lower, ×400) confirms neuroendocrine differentiation in these tumor cells

Table 5: Summary of cytomorphic spectrum of effusion with SCC and LCNEC, n = 68

	SSC, n = 53	LCNEC, n = 15
Cases with predominance of small cluster patterns	41%	73%
Cases with predominance of single-cell patterns	23%	34%
Cases with predominance of large cluster patterns	34%	0%
Cases with apoptosis at least moderate to marked	42%	100%
Cases with prominent nucleoli/multiple nucleoli	6%	86%
Cases with marked cannibalism	17%	13%

[Figures 4] was more commonly seen in this pattern (13 cases, 76%). In cell block sections from these cases, tumor cells displayed a discohesive distribution mimicking lymphoma or lymphocytosis [Figure 3]. This pattern was seen in 31% of LCNEC cases and 23% of SCC cases.

Other features such as apoptosis (karyorrhexis), nucleoli, and tumor cell cannibalism were identified in some cases of serous effusions with metastatic SCC [Figures 4-6 and Tables 4-5]. Significant apoptosis was seen in 22 cases (33%) and marked cannibalism was recorded in 11 cases (16%). Prominent nucleoli [Figures 4 and 5] were noted in 16 cases (24%), and nuclear molding was seen in 41 (60%). Ancillary studies were used in 46 cases (68%) including flow cytometric studies in 5 cases. All cases with no history of malignancy had ancillary studies to confirm the diagnosis. In most cases immunostain studies were

requested in a panel including BerEp4 or B72.3; at least one mesothelial markers (calretinin, CK 5/6, or WT-1), TTFCDx-2, ER, mamaglobin, CA125, Ki67, and one or more neuroendocrine and CD56). The most frequent neuroendocrine immunostain markers performed were synaptophysin (30 cases, 82% were positive, Figures 2 and 5) and chromogranin (30 cases, 24% were positive).

DISCUSSION

High-grade neuroendocrine carcinomas, such as SCC and LCNEC, are known for their aggressive behavior and widespread metastases. However, they are rarely reported in serous body cavity effusions.^[1-8] For example, SCC of the lung has been reported to cause a pleural effusion in less than 3% of patients.^[3] In addition, there are few published reports that discuss the cytomorphologic spectrum of SCC and LCNEC in serous effusions. To the best of our knowledge, this is the largest study to describe the cytomorphological spectrum of SCC and LCNEC in serous effusion specimens.

Our study shows that patients with SCCs or LCNECs involving serous effusions have distinct clinicopathologic features. The most common primary site where these malignancies arise is the lung (82%). Other less common sites of origin are the pancreas, cervix, colon, and head and neck. More than two-thirds of the patients in our series had no reported history of a neuroendocrine carcinoma. Of the 20 cases with a previous history of malignancy, the average interval from primary malignancy manifestation to effusion varied, with SCC having a much shorter interval compared with LCNEC.

SCC and LCNEC metastases showed a cytomorphologic spectrum within serous body cavities. Architecturally, they tend to show one of three patterns, which include a predominance of small-cell clusters (seen in both SCC and LCNEC, but more often in cases with LCNEC), a predominance of large tumor cell clusters (seen mainly in SCC), and a predominance of single tumor cells (seen in both SCC and LCNEC). About half of our cases presented predominantly with small-cell clusters. The cytological features of cases observed with a predominance of small-cell clusters have been well described in other publications.^[5,6] Malignant cells that are arranged in small clusters are 2 to 2.5 times the size of lymphocytes, with scant cytoplasm. Nuclear molding, inconspicuous nucleoli, and typical salt-and-pepper nuclear chromatin are the typical features noted in SCC. Prominent nucleoli have been reported previously mainly in LCNEC. Based on these characteristic cytomorphological, a feature along with accessory studies such as immunostains for neuroendocrine differentiation,^[3,11] the diagnosis of SCC is not difficult to make.

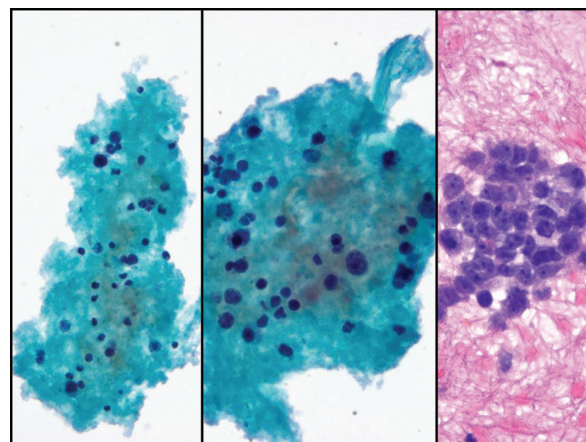


Figure 4: Small-cell carcinoma with marked apoptosis and small nucleoli seen in the Thin Prep (left and middle, Pap stain, x200 and x400, respectively) and cell block (H&E stain, x 400)

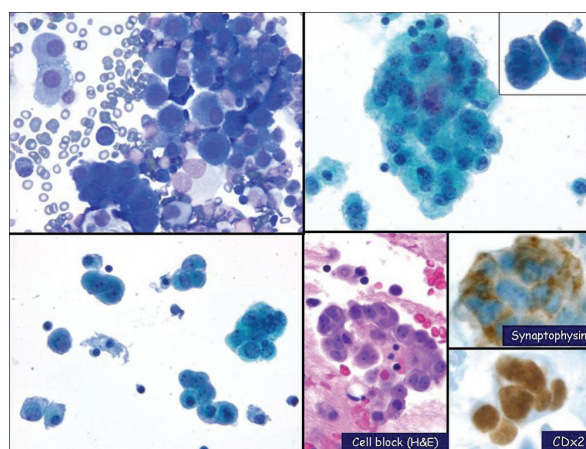


Figure 5: Large cell neuroendocrine carcinoma with prominent nucleoli shown in pleural fluid. The malignant cells have prominent nucleoli, nuclear enlargement and atypia. The cells also have a moderate amount of cytoplasm. (left upper, DQ cytosin, x400; left lower & right upper, Pap stain, x400; right lower, cell block H and E, x400; right lower, synaptophysin (top, x400) and CDX2 (bottom, x400) immunostains)

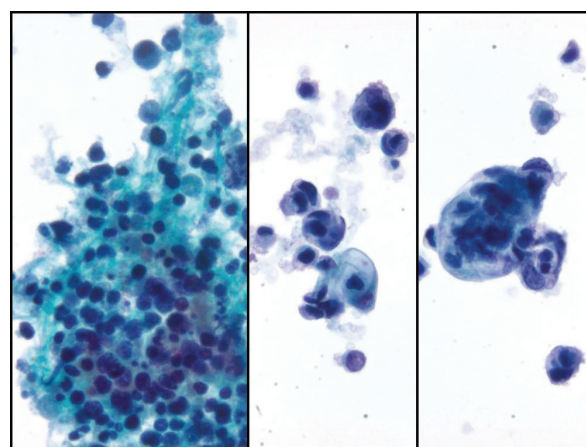


Figure 6: Cytomorphology of small-cell carcinoma showing marked apoptosis (left, Pap stain, x200) and marked cannibalism (middle and right, Pap stain, x400). [Note: Some degree of cytoplasmic vacuolization is also seen (middle and right)]

However, when malignant neuroendocrine cells present predominantly as large-cell clusters, they are likely to be misdiagnosed as adenocarcinoma based on the cytomorphology alone. This is because small tumor cells, when aggregated into large clusters in serous effusions, develop a striking architectural similarity to adenocarcinoma. In cell block sections, malignant cells produce large clusters with a hollow center, which are characteristic cytological features seen in metastatic adenocarcinoma. In addition, a few chains of small tumor cells with nuclear molding were frequently present at the periphery of the large clusters. There are a few published articles that describe the cytological features of neuroendocrine tumors that exhibit a predominance of large-cell clusters in serous effusions. Recently, Cameron *et al.* reported a case of metastatic thymic well-differentiated neuroendocrine carcinoma in pleural fluid.^[12] The cytological fluid preparation in this previously published case showed multiple large balls of malignant cells ranging in size from 150 to 376 μm . The large cannonball-type of clusters showed smooth community borders. They were composed of uniform small tumor cells without nucleoli. Some of the clusters also had a vague rosette-like arrangement. Large spherical aggregates in this prior case were also identified in the cell block sections. Cavitation of large clusters, however, was not present.^[12] A similar feature has been described^[13] in cases of mediastinal endocrine neoplasms of probable thymic origin, related to carcinoid tumor. The neoplastic clusters in these reported cases presented as large round to oval "balls" of cells, frequently observed with central necrosis and rosette formation within larger cell balls.^[13] However, to make a definite diagnosis of neuroendocrine carcinoma, immunostaining with neuroendocrine markers is required.^[3,11]

Approximately a quarter of our cases displayed a preponderance of single tumor cells in serous effusions. Karyorrhexis in such cases was commonly seen [Tables 4 and 5]. These cases mimicked non-Hodgkin's lymphoma in serous fluid.^[14,15] Rarely, other diagnoses to entertain with a predominance of single cells in serous effusions are embryonal rhabdomyosarcoma^[16] and Merkel cell carcinoma.^[17] Apart from myosin immunoreactivity and the finding of myosin-type microfilaments ultrastructurally in rhabdomyosarcoma, these sarcoma cells have characteristic convoluted nuclei without prominent nuclear molding. A CK20 immunostain with a typical perinuclear dot-like staining pattern and immunopositivity with the novel Merkel cell polyomavirus (MCPyV) marker (CM2B4) can help diagnose Merkel cell carcinoma. Cases of SCC that present with a predominance of single tumor cells are not commonly seen in serous effusions. We report 17 cases of neuroendocrine tumors with a predominance of single cells. Recently, two separate groups of researchers reported a few cases of SCC also presenting mainly with single tumor cells in serous

effusions. Khunamornpong *et al.*^[4] reported two cases of SCC of the uterine cervix in serous effusions. One of these two cases showed that almost all of the tumor cells in ascites presented with a single-cell pattern that mimics malignant lymphoma. Mitotic figures and karyorrhectic bodies in this case of cervical SCC were occasionally seen.^[4] Chhieng *et al.*^[3] reported eight cases of malignant pleural effusions due to small-cell lung carcinoma. The malignant cells in this small published series by Chhieng *et al.* reported serous effusions characterized mainly with a predominant single-cell pattern. Rare cellular aggregates were observed only in their cell block preparations. The definite diagnosis of SCC in these cases was confirmed by immunostains using synaptophysin and chromogranin.^[3] The differential diagnosis for cases in which one finds a predominance of single tumor cells in serous effusions includes SCC, lymphoma, rhabdomyosarcoma, and Merkel cell carcinoma. Immunohistochemical stains, and occasionally flow cytometry, may be crucial to definitely establish the correct diagnosis.

Finally, our data show that diagnosing LCNEC [Figure 5] is more challenging than SCC. This is due to several reasons including rare nuclear molding (only 13%), presence of a significant apoptosis (67%), and the presence of prominent nucleoli in the majority of these cases (86%). These features in LCNEC mimic poorly differentiated tumors such as adenocarcinoma. Clinical history and ancillary studies in such cases are crucial for making the proper diagnosis.

CONCLUSION

Our study reports 68 cases of SCCs or LCNECs metastatic to body fluids and predominantly occurred in patients without a history of malignancy. There were three predominant cytomorphological patterns seen in this series. The most common cytomorphological pattern observed was a predominance of small clustering of tumor cells. However, in approximately half of these cases, the pattern was either a single-cell pattern mimicking lymphoma or a large clustering pattern mimicking non-small carcinoma. Therefore, knowledge of the cytomorphological spectrum caused by neuroendocrine carcinomas in fluids may help in establishing timely and accurate diagnoses, which can help the management of afflicted patients.

COMPETING INTEREST STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors of this article declare that we qualify for authorship as

CytoJournal 2011, 8:18

defined by ICMJE. All authors are responsible for the conception of this study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT BY ALL AUTHORS

This study was conducted with approval from Institutional Review Board (IRB) at University of Pittsburgh Medical Center (UPMC), Conemaugh Memorial Medical Center, Johnstown, PA 15905, and the Department of Pathology, Fletcher Allen Health Care, Burlington, VT 05401, USA. The authors maintain relevant documentation in this respect.

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The Role of Cytology in the Management of the HIV-Infected Patient

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Prevalence of HIV

The number of people living with HIV/AIDS is increasing as more individuals now have access to antiretroviral therapy (ART). According to UNAIDS, in 2009 there were 33 million adults and children living with HIV/AIDS globally and 1.8 million related deaths.¹ While North America had only 1.5 million people living with HIV/AIDS in 2009, there is a resurgence of the HIV/AIDS epidemic due largely to infected men who have unprotected sex with men (MSM).¹

Disease Burden in HIV

HIV-infected individuals have a higher neoplastic and non-neoplastic disease burden compared to their HIV-negative counterparts. HIV virus itself can cause disease, such as persistent generalised lymphadenopathy. HIV is also associated with multinucleated giant cell formation in lymphoid and CNS tissue, as well as lymphoepithelial cysts in salivary glands (Figure 1).²⁻³ However, the majority of disease in HIV-infected individuals arises from their immunosuppression leading to opportunistic infections and neoplasia. Moreover, drug related side effects such as ART associated gynecomastia and metabolic conditions contribute to the high disease burden in the HIV-infected patient.

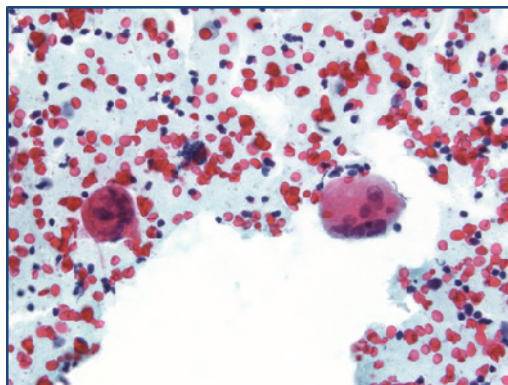


Figure 1. Multinucleated giant cells are shown in a fine needle aspirate obtained from a benign lymphoepithelial cyst-like lesion of the parotid gland in an HIV positive patient (Pap stain, high magnification).

Utility of Cytopathology

Cytology is an ideal diagnostic technique that can be used in the management of the HIV-infected patient.⁴⁻⁸ An accurate diagnosis can be rendered on a specimen that is procured in a minimally invasive manner. Minimally invasive procedures such as FNA are ideal in HIV-infected patients as they are associated with low complication rates and reduce the health care workers exposure to HIV. Cytology is also cost-effective in many circumstances; an extremely relevant consideration in both developed and low-resource communities given the current global financial situation. Another advantage of cytology is the ability to obtain a rapid result, thereby allowing timeous and appropriate treatment to be instituted in an ill patient. Many ancillary investigations such as microbiology culture, immunocytochemistry, flow cytometry and PCR can be performed on the cytology specimen. Cytology specimen types received from HIV-infected patients include cervical and anal smears, FNAs of lymph nodes and salivary glands, CSF, sputum, bronchoalveolar lavage, body fluids and brain smears.

New Developments

Mycobacterial Infection

The HIV pandemic is associated with an increased prevalence of mycobacterial infection, especially in developing countries such as Africa, Asia and South America.⁹⁻¹¹ The annual and lifetime risk of an HIV-infected patient developing tuberculosis (TB) is 10% and 50%, respectively.¹² Thus, there is significant morbidity and mortality caused by TB in HIV-infected patients. The rise in multidrug (MDR) and extreme drug resistant (XDR) TB is a worrying trend. Moreover, TB may manifest in unusual ways (e.g., spindle cell pseudotumor) in the HIV-infected patient and often presents in extrapulmonary locations. FNA has proven to be a reliable and rapid diagnostic technique in these patients. However, the confirmation of TB and other atypical mycobacterial infections may not always be straightforward. Ziehl-Neelsen staining is generally considered insensitive (40-60% when compared with culture), while TB culture can take 1 to 6 weeks for a result. Also, commercial nucleic acid amplification is less sensitive than mycobacterial culture. Given the global TB pandemic and limitations in TB diagnostics, there has been renewed interest in the development of tests that can be performed in low resource settings (e.g., TB autofluorescence, Xpert MTB/RIF assay) and those requiring sophisticated molecular laboratories with highly skilled staff (e.g., high resolution melt analysis).¹³ The utility and cost-effectiveness of these new diagnostic modalities still needs to be determined.

Non-AIDS Defining Malignancies

AIDS-defining neoplasms including Kaposi sarcoma and certain non-Hodgkin lymphomas have decreased with the use of ART. However, other malignancies have increased in HIV-infected patients despite access to ART. These non-AIDS defining cancers (NADC) are becoming an important source of illness in the HIV-infected patient.¹⁴⁻¹⁵ NADC include carcinomas (anal, vaginal, lung, oropharyngeal, colorectal, renal), Hodgkin lymphoma, seminoma, melanoma and leukemia. Risk factors for developing NADC include duration of HIV infection, patient age, lifestyle (e.g., smoking), and infection with oncogenic viruses (e.g., HPV, Merkel cell virus). Cytology plays an important role in screening for these cancers (e.g., anal Pap tests).¹⁶ Exfoliative cytology and FNA of these neoplastic lesions offer an accurate, reliable and rapid mechanism to diagnose all of these NADC, and usually provide sufficient material for ancillary studies should these be required.

Cervicovaginal Pap Tests

More women have become infected with HIV as heterosexual transmission has become the primary mode of transmission. These HIV-infected women exhibit higher rates of persistent HPV infection with multiple oncogenic viruses, more abnormal Pap tests, more prevalent cervical intraepithelial neoplasia (CIN) lesions, and aggressive invasive cervical cancer compared with HIV-negative women.¹⁷ Hence, the recommendation is that HIV-infected women should undergo more frequent Pap tests. However, the role of HPV testing in this population needs to be better defined.

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VIEWPOINT:

Cultural aspects and technical limitations of cytopathology based cervical cancer screening in India

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“Preventable but not prevented”

This is the reality of cervical cancer today, at least in developing countries like India. 80% of all the cases of cervical cancer occur in these developing countries. Worldwide, cervical cancer is the 2nd most common cancer in women and is the third most frequent cause of cancer related deaths. In India, cervical cancer is the leading cause of cancer related deaths in women. Additionally, India has the highest disease frequency, with 134,000 cases out of 530,000 worldwide (2008 statistics). Death due to cervical cancer is also high in India (73,000 deaths out of 275,000).

Cervical cancer has been extensively studied, and is known to have a very long pre-invasive phase. The Papanicolaou test (Pap) has been a time tested tool for making an early diagnosis of cervical cancer and its pre-cancerous lesions, and treating them at a stage where very high cure rates are possible. For cervical cancer prevention and early detection, the Pap test is a good screening as well as an acceptable diagnostic test. As a conventional screening test, it derives its utility from the detection of preinvasive lesions of the cervix and the identification of patients that are in need of additional diagnostic tests. As a diagnostic tool, especially in limited-resource settings, it has some utility in the cytopathological grading of samples from high risk cases, including the delineation of patients with clinically inapparent invasive carcinoma. Although the Pap test has never been shown to completely eradicate invasive cervical cancer in any society, when all components of a Pap test-based screening program are operating effectively, it certainly has been shown to reduce the incidence of and mortality associated with cervical cancer. The Pap test is the only test in our practice settings that has been used in widespread screening programs and has been conclusively shown to reduce the incidence of and mortality from cervical cancer.

However, a cancer screening program can only be effective if the targeted population has access to it and participates, the test itself combines the appropriate level of specificity and sensitivity, and the patients that are segregated for follow-up receive timely and appropriate intervention. In these respects, the Pap test and a screening program that revolves around it are most certainly not free of limitations. In India, these limitations are an amalgam of logistical, financial and socio-cultural issues. Some potential barriers to patients obtaining a Pap test and/or following up in this setting include a) a general lack of knowledge about the disease, and a lack of familiarity with the concept of the preventability of cervical cancer, b) limited public health services especially among rural sector c) lack of family support, d) geographical and economic inaccessibility to care after an “abnormal” Pap test interpretation and/or a diagnosis of cervical cancer, e) social and cultural stigma that may be associated with reproductive health problems, cancer and a ‘sexually transmitted disease’, and f) a given patient’s desire to avoid the loss of privacy that a Pap test or even a pelvic examination would entail. Even if resources are made available (for example, through a non-governmental organization-sponsored cervical cancer screening camp – figure 1), attendance is typically dismal. Women in the targeted socio-demographic profile are less likely to participate in such a program. Educated women and those who have access to health care (such as urban, higher socio-economic classes, who purportedly have a lower incidence of cervical cancer), do attend these camps, but are not the primary targets for these campaigns. Interestingly, the lowest rate of participation is in nulliparous women. In the preliminary evaluations that we have conducted, we noticed that as the parity of women increases, they were somewhat more likely to participate. Socially, this may be related to less inhibition for gynecological examination after a child birth. In a society where gynecological examinations are not routine and does not start at the teen-age groups, this is an important factor.

HPV, the major causative agent of carcinomas of the cervix, is known to be sexually transmitted. This knowledge further poses problems in cancer prevention campaigns. In India, as in many other societies, socio-cultural issues associated with sexuality between a man and woman, in and outside of marriage, remain. While sex before and outside a marriage certainly exists, screening for a disease that may provide evidence for such a relationship is an important impediment to screening. Unmarried and nulliparous women may refuse to be screened due to their fear of the social stigma that they may potentially suffer if they had a positive test result. Once in a while, a male spouse of a woman with a positive test result would request that the providing physician conduct an HPV on himself. In some instances, these relationships may be terminated based on these spousal testings.



Figure 1. Poor attendance at a well publicized cervical cancer screening camp in rural Maharashtra. Such poor attendance is not universal however (see Figure 2).



Figure 2. There is variability in responses to an invitation to a free cancer screening camp between different states within India. These may be due to cultural differences, and possibly related to educational background. Shown in this picture is a moderately well attended cervical cancer screening camp in rural Tamilnadu (Thuraiyur, Trichy district).



Figure 3. In some rural sectors of India, women are responsible for housekeeping, and hence finding time to get away from family work to attend camps, may be another limiting factor. Seen here, is a cancer screening and educational program, at a primary health center. Women often attend these camps with their children. Comprehensive family based screening for other adult and children diseases (adult: chronic kidney disease, diabetes, hypertension; children – eye & dental, deworming) is another strategy that AIPNA sponsored cancer screening programs have adopted to induce women to attend these camps.

Women who were less educated are less likely to participate in screening due to their low socioeconomic status (and the attendant difficulties in segregating the time for this activity) and their lack of familiarity with the concept of early diagnosis and prevention of cervical cancer. Accordingly, in India, poor socioeconomic status itself is a risk factor for development of cervical neoplasia.

In many of the rural areas in India, most women who come for “screening” are not asymptomatic, but rather suffer from gynecological disorders such as leucorrhoea, abdominal pain, irregular bleeding or backache. The pretest probability for a good cytological examination for a symptomatic individual is very low. Conventional cytological smears are of limited value due to heavy inflammatory infiltrate or bloody specimens in many of these cases, causing rejection of a majority of specimens. The referring physicians do not take ‘inadequate’ or sub-optimal specimen as test results, sometimes, ‘encouraging’ the cytopathologist to provide a negative test result instead (personal communication - RD).

Many places also lack the ability for proper follow up. Screening for a disease such as diabetes is more practical, where a point-of-care test (random/post-prandial blood sugar) could yield a result, which can be used for definitive counseling. Cervical cancer screening, in contrast, potentially needs follow-up after cytological examination, which may take 1-2 weeks. It may be impossible or impractical to trace back patients in some parts of rural India, for example, for a follow-up intervention after an abnormal Pap test. The ubiquitous availability of cell phones is a good means of contacting patients and is being tested in pilot camps in some instances.

Technical and interpretative errors. The absence of trained personnel, including the failure to obtain an adequate smear by the clinician, and the incorrect interpretation of the smear by inexperienced person are other potential reasons for failure in cervical cancer screening. In the absence of automated screeners, trained screening cytotechnologists represent an invaluable component of a Pap-test based screening program. Their limited availability makes cytology based screening, laborious and cumbersome for the pathologist. With rare exceptions, there are no good cytotechnologist training schools that would cater to the estimated 600 million female population of India.

In summary, reasons for failure of cervical cancer screening in India are multifactorial:

- Patients – Not participating in regularly scheduled screening, when asymptomatic. Cultural taboo of a sexually transmitted disease.
- Clinicians – Not obtaining an adequate smear; counseling of patients. Lack of follow-up or inadequate management.
- Pathologists – Lack of cytotechnologists. Lack of proficiency.
- Tumor biology – Rapidly developing invasive carcinoma.
- Health care system: Lack of good publicly funded screening programs with an outreach to target population.

Organizations such as the Association of Indian Pathologists in North America (AIPNA) have been trying to bridge the gap by organizing pilot camps, focusing on educating pathologists and clinicians and helping in upgrading pathology laboratories. The aforementioned issues are certainly not applicable to all parts of India. Nevertheless, Pap test-based screening to prevent cervical cancer in developing countries like India, remains a daunting challenge.

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PSC Election 2012, Ballot



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Dear Colleagues:

It is the time of the year for the election of officers.

The executive board has 2 positions open for 2012:
(1) Two Members-at-Large

Please check one box for the category of Treasurer and two boxes for the category of Member-at-Large. You can either email (to david.chhieng@yale.edu; the subject should be "PSC election") or fax (203-737-5388) your completed ballot to the PSC Secretary, David Chhieng. **The deadline is Dec 31st 2011.**

Member-at-Large (Check no more than two boxes)

- ☐ Ronald Balassanian
- ☐ Bill Faquin
- ☐ Fernando Schmitt
- ☐ Matthew Zarka (2nd term)

Candidates for Executive Board Member-at-large 2012



Ronald Balassanian, MD

Dr. Balassanian completed his cytopathology fellowship at University of California San Francisco (UCSF) following residency training with a surgical pathology fellowship, also at UCSF. His first year of residency training was completed at New York University. As a medical student, he completed a post-sophomore fellowship in pathology and graduated from the University of Vermont College of Medicine with a major in Surgery. Ron has a background in counseling and prior to medical school, he worked for 6 years as a Cancer Information Specialist at the Cancer Information Service, a program run by the National Cancer Institute at the Fred Hutchinson Cancer Research Center in Seattle, Washington. His undergraduate studies were completed at the University of Washington where he received dual degrees with a BS in cell biology and a BA in English Literature.

Dr. Balassanian has been a member of the PSC for several years. He was an active participant in the NCI State of the Art Thyroid FNA Conference in 2007. He is also a member of the American Society of Cytopathology and recently completed a workshop on FNA biopsy techniques at the recent 59th annual meeting. He is also a member of the United States and Canadian Academy of Pathology, the College of American Pathologists and the American Society of Clinical Pathologists. He recently joined the faculty at UCSF and is actively engaged in the FNA service. He is also working in research programs developing applications of molecular diagnostics to FNA samples. He is also a co-investigator for the Athena Breast Health Network, a collaborative project between the 6 University of California medical centers which seeks to set standards for diagnosis and treatment of breast cancer.

Dr. Balassanian has had the privilege to work in many different pathology laboratories with varying approaches to cytology and FNA, ranging from cytology as a screening assay to a cytology as a definitively diagnostic sample. Prior to UCSF, he worked at Massachusetts General Hospital where his primary focus was on the FNA service. Prior to MGH, he was at the University of Pittsburgh/UPMC and was the director of the FNA clinic. He has also worked at Beth Israel Cancer Center in NY, and Weil Cornell-New York Presbyterian Hospital. Based on these experiences, Ron has seen first hand the diversity of practice standards in cytopathology. Each experience has presented unique opportunities for learning and development. Ron believes variation in diagnosis and practice standards across the country and the world, is one of the great challenges in our field. In fulfilling its mission to bridge the gap between surgical pathology and cytopathology, the PSC is poised to play a critical role in education and harmonization among the community of cytopathologists, and surgical pathologists. Moreover, Ron sees the broader ramifications of this mission for the patient: in an age when patients rightly demand less invasive treatment and diagnosis, with targeted molecular assays and gene sequencing, the PSC, by fulfilling expanding its mission, has an exciting opportunity to connect the patient and the pathology lab.



William C. Faquin, MD, PhD

As a candidate for the Executive Board, Dr. Faquin will strongly support the mission of the PSC to promote high standards in the practice and teaching of cytopathology. He received his training in pathology and cytopathology at the Brigham and Women's Hospital, and is a cytopathologist and Chief of Head and Neck pathology at the Massachusetts General Hospital and the Massachusetts Eye and Ear Infirmary in Boston. He has been an active member of the PSC for the past 13 years, and has served on the PSC's Scientific Program Committee, the Membership Committee, the Budget and Finance Committee, the Awards Committee, and the Practice Guidelines Committee for Thyroid Cytopathology. In an effort to promote teaching of cytopathology, he has lectured extensively, and directed courses and workshops both nationally and internationally in the field of head and neck cytology. If elected to the PSC executive board, he will work hard to ensure that the PSC continues its leading role in advancing the field of cytopathology through its policies, its educational programs, and its national and global

outreach.



Fernando Schmitt, MD, PhD

Dr. Schmitt is a Professor of Pathology at the University of Porto, Portugal and serves as the Medical Director of the Unit of Pathology at Institute of Pathology and Immunology of Porto University (IPATIMUP). He received his medical degree from the University of Santa Maria (Brazil) in 1983. Fernando served his pathology residency at the Medical Faculty of Botucatu, São Paulo and after a fellowship in Clinical Cytology at Karolinska Medical Hospital, Stockholm under the supervision of Torsten Lowagen and Lambert Skoog; he developed an aspiration clinic at University Hospital in SP and earned his PhD in Pathology in 1990.

After ten years in the University of São Paulo, Fernando moved to Portugal in 1993. He established a research group in breast pathology and a FNA service at IPATIMUP. As Director of the Unit of Pathology he prepared this Unit and got the CAP accreditation making the only anatomic pathology lab accredited by CAP in Iberia peninsula.

Dr. Schmitt holds 20 national and international society memberships, including FIAC obtained after examination in 2006. Dr. Schmitt has authored more than 509 papers in peer-review journal and 17 book chapters and has presented widely on cytologic and breast cancer subjects. He serves as Associate Editor of Diagnostic Cytopathology, Acta Cytologica and BMC Cancer and belongs on the Editorial board for a number of journals (Breast Cancer Research, Cytopathology, Journal of Clinical Pathology, Pathology Research and Practice, Virchows Archives, among others). Dr. Schmitt has served on various national and international committees of Pathology and Cytology Societies. He was chairman of the Working Group of Cytopathology of the European Society of Pathology (ESP) during six years, past- president of the Portuguese Society of Cytology during four years and scientific director of the Brazilian Society of Cytology for four years. Actually, he is General Secretary of the International Academy of Cytology (IAC) and Past- President of the European Federation of Cytology Societies (EFCS). He organized several slide seminars, courses and other activities related to cytology and breast pathology in the last European congresses of Pathology and Cytology and were the President of the 35th European Congress of Cytology realized in Lisbon in September 2009.

His main areas of research are molecular markers in cytology, cell adhesion and invasion in breast cancer as well as the study of therapeutic targets and mechanisms of resistance. He was recently awarded as Educator of the Year 2011 by the Papanicolaou Society of Cytology. Teaching medical students, research in breast pathology and diagnostic on FNA are his favorite's activities at this moment.

Matthew A. Zarka, MD



Dr. Matthew A. Zarka obtained his medical degree from St. Louis University and completed his residency training in Anatomic Pathology at University of California San Francisco in 1990. After fellowship training in Cytopathology at UCSF in 1991, he began his pathology practice in Stockton, CA. He returned to academic medicine in 1994, joining the faculty at the UVM College of Medicine in Burlington, VT. At UVM he served as Director of Cytopathology and Anatomic Pathology until 2000. Dr. Zarka is currently a Consultant in Laboratory Medicine and Pathology at Mayo Clinic Arizona in Scottsdale, Arizona and serves as Director of Cytopathology.

Dr. Zarka studied fine needle aspiration biopsy at the Karolinska Institute with Dr. Torsten Lowhagen. He has served on the Technical Advisory Group on Comprehensive Cervical Cancer Control at the World Health Organization in Geneva, Switzerland and reviews original submissions for several medical journals including Cancer, Cancer Cytopathology, Diagnostic Cytopathology, and Archives of Pathology and Laboratory Medicine. He has given numerous invited presentations and microscope workshops on the interpretation of fine needle aspiration biopsy and GYN cytology, nationally and internationally. He has served as Medical Director of Grounds for Health, a non-profit organization promoting cervical cancer screening in rural areas of Mexico and Central America, and is a proponent of traditional cytologic screening for cervical cancer in developing countries. He has participated in FNA tutorials with Dr. Andrew Field in Sub Saharan Africa under the auspices of the Papanicolaou Society, and was awarded the 2010 Humanitarian Grant from the College of American Pathologist Foundation for this effort. He currently serves on College of American Pathologists Foundation. He is the current Chair of the Scientific Program Committee of the Papanicolaou Society of Cytopathology and is seeking a second term as a member-at-large of the PSC Executive Committee. He is a strong advocate of charitable support for education, research, and humanitarian programs related to pathology.

Dr. Zarka is a strong advocate of charitable support for education, research, and humanitarian programs related to pathology. He will continue to advocate that the PSC expand its influence on an international level and support philanthropic projects in the developing world.

Papanicolaou Society of Cytopathology USCAP Companion Society Activities

Vancouver Convention Center, Vancouver, British Columbia

March 17th 2012

10:30am-1pm Papanicolaou Society Executive Board Meeting (Officers and Executive Board only)
Location: **Pan Pacific Vancouver Hotel: Oceanview Suite 7**

2:00-4:00pm INTERNATIONAL RELATIONS COMMITTEE AFTERNOON SESSION
Location: **Pan Pacific Vancouver Hotel: Oceanview Suite 7**
Moderator: Dr. Eric Suba, Kaiser Permanente

2:00-2:30pm The natural history of human papillomavirus as the rational basis for cervical cancer prevention
Speaker: Dr. Philip Castle, American Society for Clinical Pathology Institute

2:30-3:00pm Visual screening methods for cervical neoplasia
Speaker: Dr. Vivien Tsu, Program for Appropriate Technology in Health

3:00-3:30pm Experience with careHPV testing in three developing countries
Speaker: Dr. Jose Jeronimo, Program for Appropriate Technology in Health

3:30-4:00pm Action plan for improving lab services in resource-constrained settings
Speakers: Roundtable discussion with audience participation

4:00-5:00pm ANNUAL BUSINESS MEETING
Location: **Pan Pacific Vancouver Hotel: Oceanview Suite 7**

5:00-7:00pm COCKTAIL RECEPTION
Location: **Pan Pacific Vancouver Hotel: Oceanview Suite 3**

7:00-10:00pm: PAPANICOLAOU COMPANION SOCIETY EVENING SESSION
**"Diagnosing Lung Carcinoma in the Era of Personalized Medicine:
Clinical, Pathologic, and Molecular Aspects"**
Location: **Vancouver Convention Center**

7:00-7:15pm Welcome and Award Presentation
Speaker: Dr. Lester Layfield, University of Utah
Introduction of program and panelists
Speaker: Dr. Matthew A. Zarka, Mayo Clinic

7:15-7:50pm Clinical approach to cytologic and histologic sampling in the patient with lung cancer
Speaker: Dr. Robert Viggiano, Mayo Clinic

7:50-8:25pm Practical approach to the diagnosis and management of nonsmall cell lung cancer encountered in limited biopsy samples (transbronchial and needle core).
Speaker: Dr. Kevin O. Leslie, Mayo Clinic

8:25-9:00pm Respiratory tract cytology: from basic morphology to advanced molecular analysis.
Speaker: Dr. Kim R. Geisinger, Wake Forest Baptist Medical Center

**9:00-9:35pm AMP-CAP-IASLC guidelines for molecular testing of lung adenocarcinoma :
Who to test, why to test, and how to test?**
Speaker: Dr. Neil I. Linderman, Brigham & Women's Hospital

9:35-10:00pm Question and Answer session

News & Announcements

PSC Membership Application Form



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Dear Colleague:

It is the time of year again to renew your PSC membership.

We have a wonderful year planned for 2012, which includes 2 issues of FOCUS and the Evening Companion Meeting at the USCAP in Vancouver BC Canada which will begin at 7:00 PM on March 17th 2012. The theme will be **"Diagnosing lung carcinoma in the era of personalized medicine: clinical, pathologic, and molecular aspects."** On the same day, the PSC will also have an afternoon session "Cells without borders" organized by PSC International Relations Committee. Please see the accompanying flyer for more details.

*****Please make sure you pay your dues by January 30, 2012.*****

This will assure you of mailings of all our information for the coming year and your subscription to DIAGNOSTIC CYTOPATHOLOGY.

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