The International System for Serous Fluid Cytopathology

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Editors

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To my great mentors – Professor Monisha Choudhury, Professor Dulcie Coleman and Dr Amanda Herbert – for their inspiration and encouragement through my early years in cytopathology. AC

To my mother, for giving me freedom to explore, and to the cytopathology community for their cohesion, dedication and unflagging commitment to patients and their health through cytopathology. BC

To my father, Frank Kurtycz, a family man and veteran, who educated three generations of descendants and provided us a model of honor and care. DK

To all who helped, taught and supported me during my scientific career. FS

Foreword

Whilst the pendulum of cytopathology as a diagnostic modality in different organs and systems, through the years, swung both ways, its use in the diagnosis of serous fluids has never been in question. It has stood the test of time as a universally accepted method contributing to clinical management, either in primary diagnosis, staging or follow-up settings. As such, it represents a high proportion of routine specimens in an average diagnostic cytopathology laboratory. Whether a single drop or litres of it, serous fluid is a familiar sample to all cytopathologists and cytotechnologists around the world.

Observing a cytopathologist at work, a fly on the wall might consider our job sedentary and dull. Taking that view, we could compare cytopathology to snorkelling: looking from the shore, a slow moving, breathing tube of a diver on the surface of the water may appear boring, not appreciating that there is a whole underwater planet there to explore. And, drawing a parallel, through the microscope, we are exploring a 'planet body'. There, amongst the cells encountered, those in the serous fluids remind us most vividly of a life submerged under water. Cells float freely, with their tentacle-like processes, unimpeded by the artefacts of other cells obtained by means of brushing, scraping or aspirating. Transporting these delicate cells from the fluid onto a glass slide, in a perfect state of preservation, ready to be observed under a microscope, involves the masterly skill of a cytotechnologist. Excelling in and developing various preparatory techniques should not be underestimated and ultimately can make a major difference between success and failure in their recognition and interpretation.

The interpretation of microscopic findings in serous fluid is challenging. It is often the most difficult part of a trainee cytopathologists' preparation for the final specialist examination/board certification. Unfortunately, it does not end there. It gets worse later when, as a specialist, the interpretation is equally difficult except one's opinion, confirmed by the signature at the bottom of the report, now makes a real life difference to clinical management. This can be a frightening experience if you have no language of communication or coding to convey areas of concern. It is estimated that around one third of serous fluids are difficult to assess by morphology alone, but it takes time to accept one's shortcomings. In the past, the main mode of clinical communication was interpreting cells as 'malignant' or 'not malignant', to the extent that many laboratories had a rubber stamp stating these crude options. This approach reduced cytopathology to issuing machine-like results that were

lacking detail and did not allow for grey areas. The use of immunocytochemistry and other ancillary techniques has helped confirm and refine the diagnosis and is now commonplace. Its use is an expected gold standard for the reporting of serous fluids. Laboratories that do not have these facilities available should consider sharing with a larger laboratory rather than giving up on the opportunity of reaching the correct answer.

The International System of Reporting of Serous Fluids (TIS), described in this book, is a new language of communicating the result between the cytopathologist and the clinical team. It should help in all, including the most difficult cases, by stratifying the diagnostic certainty. TIS defines a spectrum of diagnostic categories to be used in daily clinical practice, allowing for doubt and recognising diagnostic dilemmas which sometimes, despite our best efforts, cannot be avoided. Although, for ease of communication, it is a numerical system, partly a nod to our elders who used it in other areas of cytopathology, it is not intended as a substitute for a full diagnostic description, only making the interpretation easier in terms of clinical management. TIS also incorporates the concept of 'risk of malignancy' (ROM) for different diagnostic categories, which has thus far been used successfully elsewhere in cytopathology and adds an important lever to a clinical dialogue which is required more and more frequently.

Communication between the laboratory and the clinic has several aspects, all of which are important. One of the key ones is *clarity*. Nowadays, when formal meetings between the laboratory and clinical teams are held via digital media, communication has to be particularly streamlined to avoid any misunderstanding. TIS addresses the diagnostic part of this communication, serving as a template to aid in patient management. It lends itself to clearer Clinical Management Guidelines. When issuing a TIS report, cytopathologists should be aware of the clinical management protocols and the role their diagnosis plays in it. Ideally, the findings should be discussed with the multidisciplinary clinical team regularly.

In addition to the advantages to direct patient care, the widespread use of TIS will have other benefits, such as a role in collaborative research by making data between laboratories comparable, contributing to easier evaluation of outcomes/audit/follow-up protocols and elucidating teaching conundrums, amongst others.

Looking at cells with our diving mask/microscope, they will still not be labelled with numbers or ROM percentages. In daily practice, the final result will still depend on *expert preparation*, *careful interpretation* using all available ancillary techniques and a *clear*, if sometimes not definitive, *conclusion*, communicated via the new TIS language including a numerical category. With this triumvirate, serous fluid cytopathology should remain one of the most used diagnostic investigations to make a substantial contribution to clinical management.

Cavtat, Croatia Gabrijela Kocjan

Preface

This project was a collaborative effort between the International Academy of Cytology (IAC) and the American Society for Cytopathology (ASC) and called upon participation of the international cytopathology and oncology communities to contribute to the development of a truly international system for reporting serous fluid cytology. The project was conceptualized when the authors recognized that cytopathology reporting terminology had been developed and highly adopted for nearly all body sites with the glaring exception of serous fluids. Moreover, the expanding global medical environment necessitated a common language for pathology reporting to ensure appropriate patient management.

The authors organized task forces around each of the book chapters comprised of international experts in those areas, which included 41 individuals from 18 countries. An initial current practices survey was released on the Internet to members of the IAC and ASC, which was used to formulate initial consensus nomenclature and recommendations. A second Internet-based survey of gynecologic oncologists was released through the Society of Gynecologic Oncology to investigate clinical preferences for reporting and uses of peritoneal cytopathology in practice. Among the many challenges faced by the task forces was the lack of evidence-based data to support current practices and proposed changes, but implementation of a baseline standard serous fluid terminology should potentiate further studies and allow for future alterations. The authors also recognized special challenges in serous fluid cytopathology, such as reporting the presence of Mullerian epithelium in peritoneal fluids. What is an appropriate serous fluid volume to ensure adequacy? How should mesothelial proliferations be reported and is it appropriate to make an interpretation of malignant mesothelioma? How specific should a report be regarding the origin and subtyping of tumors found in serous fluids? What are the appropriate quality monitors for this specimen type? Special chapters on considerations for peritoneal washings, cytopreparatory techniques, mesothelioma, and quality management are included to address these issues. Lead authors for each chapter performed literature reviews to eludidate existing evidence in support of current practices and recommendations. Where evidence was lacking, the most common practices were adopted by consensus, and where there was no commonality, expert opinion was employed.

This terminology uses a 5-tier framework of categories that is familiar and popularized by preceding cytopathology terminology systems: nondiagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS),

suspicious for malignancy (SFM), and malignant (MAL). Because the majority of tumors involving serous fluids are metastatic adenocarcinoma, further qualification of tumor cell differentiation and/or primary site are important clinically and the chapter on ancillary studies addresses the importance of additional evaluation. The appropriate clinical management for findings is not specifically addressed in most chapters due to the diversity of possible tumor types recovered.

In an ideal situation, consensus terminology would be widely implemented, supported, and evidence-based, but there must be a starting point, and we hope that this effort will serve as a baseline for international comparative research on outcomes based on its use.

London, UK — Ashish Chandra
Silver Spring, MD, USA — Barbara Crothers

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Abbreviations

ADASP	Association of Directors of Anatomic and Surgical Pathology
ADC	Adenocarcinoma
ADx-ARMS	ADx amplification refractory mutation system
AEC	3-amino-9-ethylcarbazole
AFB	Acid fast bacillus
AFP	Alpha fetoprotein
AGCT	Adult granulosa cell tumor
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AMP	Association for Molecular Pathology
AP	Anatomic pathology
APC	Allophycocyanin
ARID1A	AT-rich interaction domain 1A
ASC	American Society of Cytopathology
ASCO	American Society of Clinical Oncology
AUS	Atypia of undetermined significance
BAP1	BRCA1 associated protein 1
BCL2/6	B cell lymphoma 2/6
bFGF	Basic fibroblast growth factor
BRCA	Breast cancer (type 1 or 2) gene susceptibility protein
CAIX	Carbonic anhydrase IX
CAF	Cancer-associated fibroblasts
CAP	College of American Pathologists
CAPP-Seq	Cancer Personalized Profiling by Deep Sequencing
CB	Cell block
CCC	Clear cell carcinoma
CD	Cluster designation
CDKN2A	Cyclin-dependent kinase inhibitor 2A protein
CEA	Carcinoembryonic antigen
CEP	Chromosome enumeration probes
CF	Cytocentrifugation
cfDNA	Cell free DNA

CHC	Cytology-histology correlation
CK	Cytokeratin
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLL	Chronic lymphocytic leukemia
CMS	Centers for Medicare and Medicaid Services
CALT	Coelom-associated lymphoid tissue
CS	Cytospin™
CT	Computed tomography
DAB	Diaminobenzidine
DAPI	4,6-diamidino, 2-phenylindole dihydrochloride
DLBCL	Diffuse large B-cell lymphoma
DMM	Diffuse malignant mesothelioma
DNA	Deoxyribonucleic acid
DPAM	Disseminated peritoneal adenomucinosis
dPCR	Digital polymerase chain reaction
DS	Direct smear
DQ	Diff-Quik stain
EBER	Epstein-Barr virus-encoded small RNAs
EBT	Endometrioid borderline tumor
ECA	Endocervical adenocarcinoma
ECCC	Endometrial clear cell carcinoma
EGFR	Epidermal growth factor receptor
EGR	Early growth response factor
EMA	Epithelial membrane antigen
EPP	Extrapleural pneumonectomy
EQA	External quality assurance, European Quality Assurance
ER	Estrogen receptor
FDA	Food and Drug Administration
FC	Flow cytometry
FFPE	Formalin fixed, paraffin embedded
Fig.	Figure
FIGO	Federation International of Gynecologists and Obstetricians
FISH	Fluorescent in situ hybridization
FNA	Fine needle aspiration
FTA	Flinders Technology Associate
GATA3	GATA binding protein 3
GCDFP15	Gross cystic disease fluid protein 15
GMS	Grocott's methenamine silver stain
HCG	Human chorionic gonadotropin
H&E	Hematoxylin and eosin stain
HER2	Human epidermal growth factor receptor 2
HG	HistoGel
HLA	Human leukocyte antigen
HGEC	High grade endometrioid carcinoma
HGMC	High grade mucinous carcinoma

HGSC	High grade serous carcinoma
HGSOC	High grade serous ovarian carcinoma
HHV8	Human Herpes virus 8
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HMB45	Human Melanoma Black 45
HMWK	High molecular weight keratin
HNF1	Hepatocyte nuclear factor 1
H/RS	Hodgkin/Reed Sternberg cell
IAC	International Academy of Cytology
IASLC	International Association for the Study of Lung Cancer
IC	Immunochemistry
ISH	In situ hybridization
ISO	International Organization of Standardization
JGCT	Juvenile granulosa cell tumor
kD	Kilodalton
LAP	Laboratory Accreditation Program
LBC	Liquid based cytology
LBL	Lymphoblastic lymphoma
LBP	Liquid based preparation
LCM	Laser capture microdissection
LE	Lupus erythematosus
LGEC	Low grade endometrioid carcinoma
LGSC	Low grade serous carcinoma
LIS	Laboratory information system
LM	Localized mesothelioma
LMWK	Low molecular weight keratin
MAL	Malignant
MAL-P	Malignant (Primary)
MAL-S	Malignant (Secondary)
MALT	Mucosa-associated lymphoid tissue
ME	Malignant effusion
MET	Mesenchymal-epithelial-transition
MBT	Mucinous borderline tumor
MGB	Mammaglobin
MGG	May-Grünwald Giemsa
mL	Milliliter
MM	Malignant mesothelioma
MMMT	Malignant Müllerian mixed tumor
MMR	Mismatch repair
MMT	Mesothelial-mesenchymal transition
MPSC	Micropapillary serous carcinoma
MSI	Microsatellite instability
MSS	Microsatellite stable
MT	Molecular testing

MTAP	Methylthioadenosine phosphorylase
MUC	Mucin protein
MUM1	Multiple myeloma 1
MZL	Marginal zone lymphoma
N:C	Nuclear to cytoplasmic ratio
NCB	Needle core biopsy
NCCN	National Comprehensive Cancer Network
ND	Nondiagnostic
NE	Neuroendocrine
NEC	Neuroendocrine carcinoma
NHL	Non-Hodgkin lymphoma
NFM	Negative for malignancy
NGS	Next generation sequencing
NOS	Not otherwise specified
NSCLC	Non-small cell carcinoma lung
NTRK	Neutrotrophic receptor tyrosine kinase
OCCC	Ovarian clear cell carcinoma
OCT3/4	Octamer binding transcription factor 3/4
PanK	Pancytokeratin
Pap	Papanicolaou stain
PAS	Periodic acid Schiff
PASD	Periodic acid Schiff with diastase
PAX	Paired box gene protein
PCR	Polymerase chain reaction
PD-L1	Programmed cell death ligand 1
PEL	Primary effusion lymphoma
PET	Positron emission tomography
PIC	Peritoneal inclusion cyst
PLAP	Placental alkaline phosphatase
PMP	Pseudomyxoma peritonei
PR	Progesterone receptor
PSA	Prostate specific antigen
PSAP	Prostate specific acid phosphatase
PT	Plasma thrombin
QA	Quality assurance
QC	Quality control
QI	Quality improvement
QM	Quality management
RCC	Renal cell carcinoma
RET	Rearranged during transfection
RM	Reactive mesothelium
RNA	Ribonucleic acid
ROM	Risk of malignancy
ROSE	Rapid on site evaluation
RPM	Revolutions per minute

RPMI	Roswell Park Memorial Institute medium
RS	Reed Sternberg cell
RT-PCR	Reverse transcriptase polymerase chain reaction
SALC	Serosa-associated lymphoid clusters
SALL4	Sal-like protein 4
SATB2	Special AT-rich sequence-binding protein 2
SBT	Serous borderline tumor
SCC	Squamous cell carcinoma
SEC	Serous endometrial carcinoma
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SFM	Suspicious for malignancy
SMA	Smooth muscle actin
SMRP	Soluble mesothelin related peptides
SmCC	Small cell carcinoma
SP	SurePath™ liquid based preparation
STAMP	Sequence tag-based analysis of microbial population dynamics
STIC	Serous tubal intraepithelial carcinomas
TAG	Tumor associated glycoprotein
TAT	Turnaround time
TBS	The Bethesda system
TIS	The International System for Reporting Serous Fluid Cytopathology
TJC	The Joint Commission
TKI	Tyrosine kinase inhibitor
TP	ThinPrep® liquid based preparation
TPS	Tumor proportion score
TTF1	Thyroid transcription factor-1
UK NEQAS	United Kingdom National External Quality Assessment Service
US	United States
VEGF	Vascular endothelial growth factor
WDPM	Well differentiated papillary mesothelioma
WHO	World Health Organization
WT1	Wilms' tumor 1
YST	Yolk sac tumor