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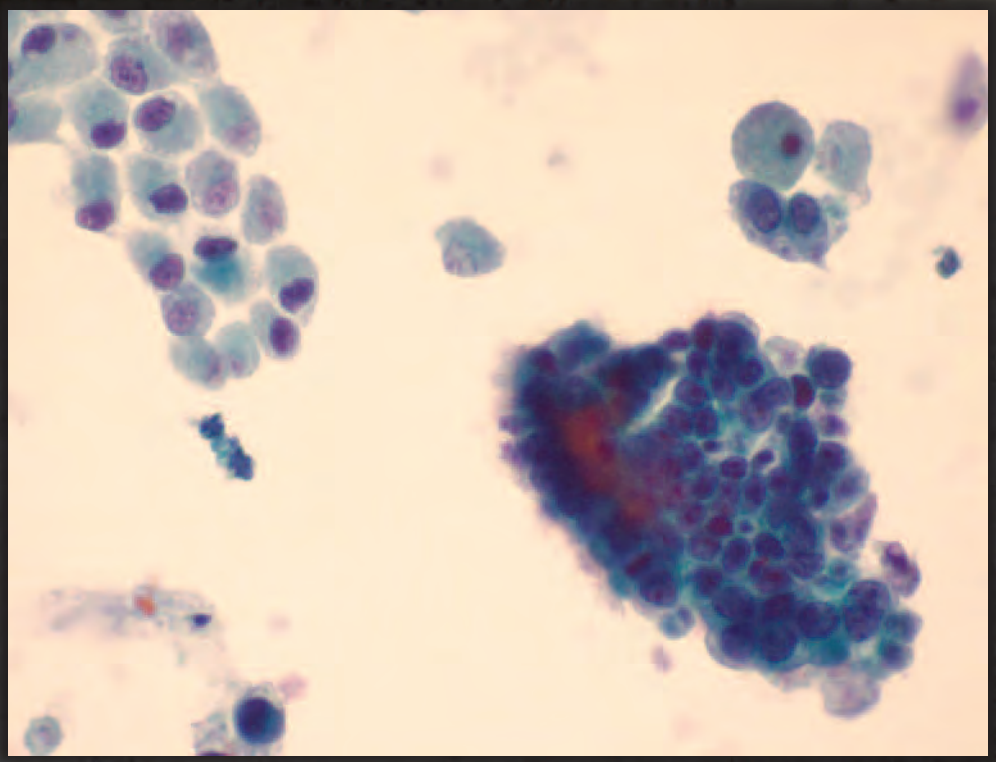

Pathological Reporting of Colorectal Polyps: Pan-Canadian Consensus Guidelines

Review of Peritoneal Washings: Diagnostic Challenges and Pitfalls

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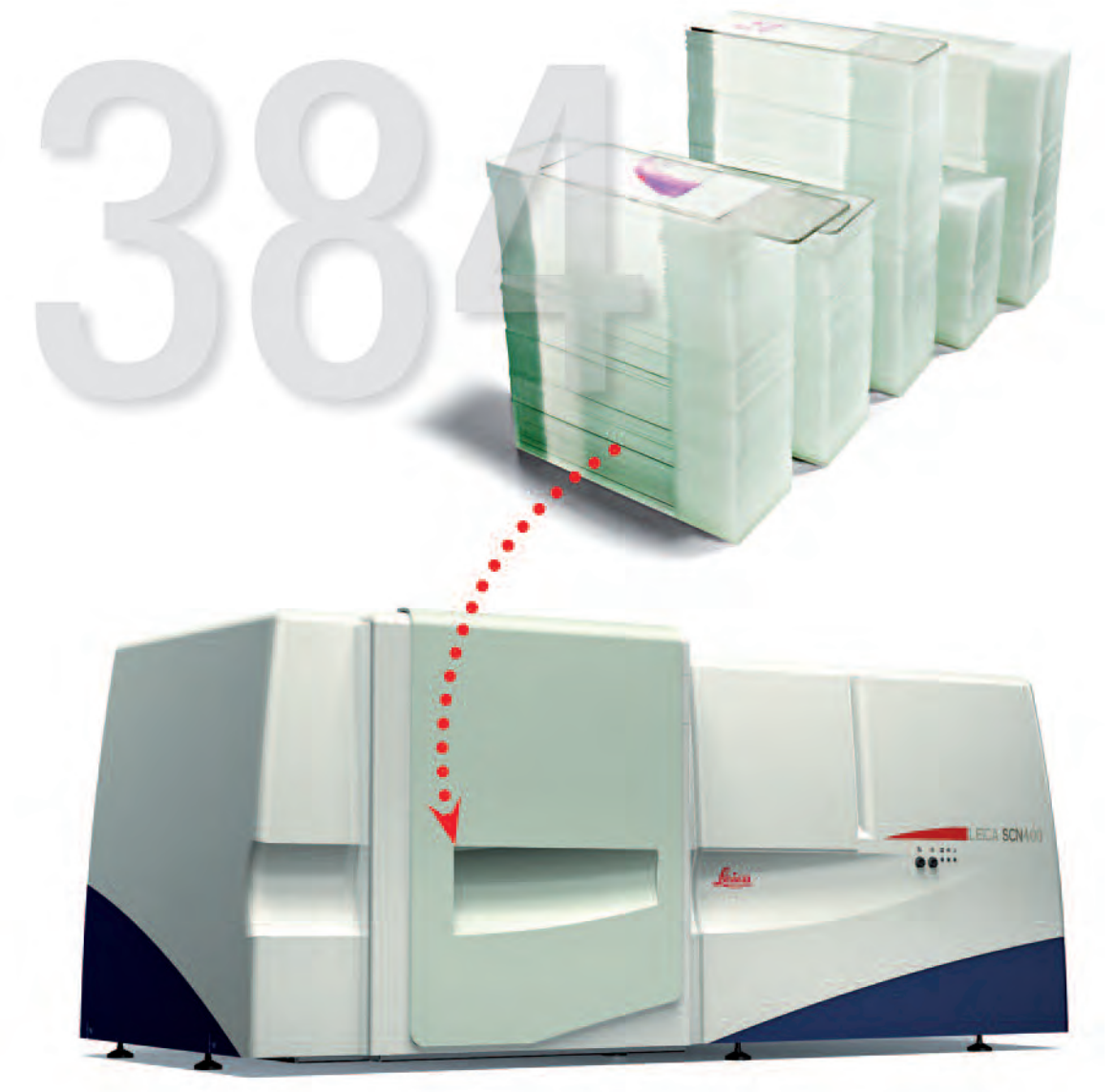

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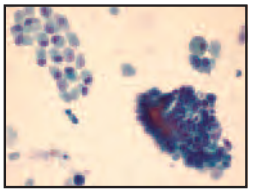

The cover image shows a benign mimic of malignancy in peritoneal washings – ciliated epithelium.

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EDITORIAL

Diagnosis of Colorectal Polyps

Colorectal cancer (CRC) is the number two cause of cancer death in Canadians, yet the vast majority of CRCs are preventable if detected early. Presently, all 10 Canadian provinces and one territory have introduced CRC screening programs. Accurate diagnosis of colorectal polyps by surgical pathologists is a key component of the success of these cancer-prevention initiatives, but our reports do not always provide all the information necessary for optimal patient management. The terminology can be confusing and variable among pathologists, and there is inconsistent application of diagnostic criteria.

After an inclusive consultation process, a group of pathologists, gastroenterologists, and members of the Canadian Partnership Against Cancer (CPAC) representing all 10 Canadian provinces developed practical consensus guidelines for reporting colorectal adenomatous and serrated polyps. These guidelines, which are published in this issue of the *Canadian Journal of Pathology* (see pp. 81–90), include clear definitions, address confusing terminology, recommend standardized reporting, and provide instructive images. Methods for optimal specimen handling and processing, as well as a summary of general clinical management and surveillance, are included.

The diagnosis of high-grade dysplasia (HGD) in adenomatous polyps has important implications for surveillance. The consensus document includes well-chosen images that clearly illustrate critical diagnostic criteria to distinguish low- from high-grade dysplasia. The accompanying discussion also highlights the importance of architectural complexity in HGD. The authors list several potential pitfalls that may lead one to overdiagnose HGD. Adenomatous polyps without HGD should include the phrase *negative for high-grade dysplasia and malignancy* and should not use the term *positive for low-grade dysplasia* to avoid potential confusion and overtreatment. Similarly, the implications of the subjective assessment of "villosity" are addressed. Small samples of large polyps with focal villous architecture are best reported as *at least tubulovillous*. Undoubtedly, the most confusing aspect for both clinicians and pathologists regards serrated polyps. Although the group did not reach a consensus on the best term for sessile serrated (SS) lesions (both *SS adenoma* and *SS polyp* are acceptable terms), it was recommended that the diagnosis of all SS lesions include *negative for dysplasia* or *with dysplasia*. The controversial prefixes *conventional* and *cytological* pertaining to dysplasia are not recommended. Any SS lesion with dysplasia is considered an advanced lesion. The group provides an example of a comment that should be included in the report to alert the clinician to the increased risk of adenocarcinoma and the importance of endoscopic removal. When reporting malignant polyps, it is critical to include the tumour grade, the presence or absence of lymphovascular invasion, and resection margin status. These factors have major clinical implications both for prognosis and surgical management.

This pan-Canadian consensus provides surgical pathologists with recommendations for reporting colorectal adenomatous and serrated polyps and clarifies confusing terminology. Achieving consensus on these issues is a major achievement that will result in clearer communication to clinicians, more accurate diagnosis, and more appropriate patient management. It also opens the door to national comparative studies. Now is the time to incorporate these recommendations into our routine practice and to monitor our progress. The responsibility falls on us as a community of pathologists to ensure rapid uptake of these guidelines to realize their potential benefits. We can now speak the same language; it is time to spread the word.

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Le diagnostic des polypes colorectaux

Le cancer colorectal est la deuxième cause de décès par cancer au Canada; pourtant, il est possible de l'éviter dans la majorité des cas s'il est détecté tôt. Les dix provinces et un territoire du pays se sont dotés d'un programme de dépistage du cancer colorectal. La réussite de ces initiatives de prévention du cancer repose pour beaucoup sur le diagnostic précis du polype colorectal par le pathologiste clinicien; or, le rapport d'examen ne renferme pas toujours tous les renseignements nécessaires pour optimiser la prise en charge du patient. La terminologie peut prêter à confusion, sans compter qu'elle n'est pas forcément la même d'un pathologiste à un autre et que l'application des critères diagnostiques n'est pas uniforme.

Après une vaste consultation, un groupe de pathologistes, de gastroentérologues et de membres du Partenariat canadien contre le cancer représentant les 10 provinces canadiennes ont rédigé des lignes directrices sur le compte rendu d'examen et la classification des polypes adénomateux et des polypes festonnés. Ces lignes directrices, publiées dans le présent numéro de *Canadian Journal of Pathology* (p. 81–90) renferment des définitions précises, se penchent sur la question de la terminologie ambiguë, recommandent des normes de présentation des résultats de l'examen et sont illustrées d'images instructives. Elles abordent également la manutention et le traitement du prélèvement et proposent un résumé de la prise en charge et de la surveillance cliniques en général.

Le diagnostic de polype adénomateux dysplasique de haut degré de malignité revêt de l'importance en ce qu'il a des suites du point de vue de la surveillance. Les lignes directrices renferment des images qui illustrent parfaitement les critères diagnostiques permettant d'établir la distinction entre la dysplasie de faible degré de malignité et la dysplasie de haut degré de malignité. Elles soulignent les aspects architecturaux complexes des lésions dysplasiques de haut degré de malignité. Les auteurs mettent en garde contre certains écueils qui risquent de dérouter le diagnostic. Le rapport d'examen du polype adénomateux hors de la catégorie de haut degré de malignité devrait porter la mention que voici : *résultat négatif pour ce qui est de la dysplasie de haut degré de malignité* de préférence à la mention d'un *résultat positif pour ce qui est de la dysplasie de faible degré de malignité* afin d'éviter toute confusion et un traitement excessif. De même, l'évaluation subjective de l'aspect « villeux » est abordée. Le compte rendu de l'examen du prélèvement de petite taille de gros polypes au contingent villeux limité devrait indiquer la présence d'adénomes *tubulovilleux à tout le moins*. L'adénome festonné représente indéniablement la lésion la plus difficile à classer pour les cliniciens et les pathologistes. Bien que le groupe ne s'entende pas sur le meilleur terme pour désigner la lésion sessile festonnée (*adénome sessile festonné* et *polype sessile festonné* sont deux termes acceptables), il recommande de préciser le diagnostic de ces lésions sessiles festonnées comme suit : *résultat négatif pour ce qui est de la dysplasie* ou *présence de dysplasie*. Les qualificatifs controversés *classique* et *cytologique* accolés au terme de dysplasie sont à éviter. Toute lésion sessile festonnée caractérisée par la dysplasie est considérée comme une lésion avancée. Le groupe présente un exemple d'observations qui devraient figurer dans le rapport afin de prévenir le clinicien du risque accru d'adénocarcinome et de souligner l'importance de l'excision endoscopique. Lorsque l'examen révèle des polypes malins, le rapport d'examen doit impérativement indiquer le degré de différenciation, la présence ou l'absence de propagation lymphovasculaire et l'état de la marge de résection. Ces aspects revêtent énormément d'importance dans l'établissement du pronostic et la prise en charge chirurgicale.

Ces lignes directrices consensuelles ont le mérite d'encadrer l'examen des adénomes et des polypes festonnés colorectaux et de préciser la terminologie. Ce consensus constitue un progrès remarquable qui améliorera la communication avec les cliniciens, l'exactitude diagnostique et la prise en charge du patient. En outre, il prépare le terrain en vue de l'exécution d'études comparatives d'envergure pancanadienne. Il ne nous reste qu'à mettre en application ces recommandations et à surveiller le changement qui s'opérera. Il nous revient donc, à nous les pathologistes, de voir à l'adoption rapide de ces lignes directrices pour en retirer les avantages promis. Maintenant que nous pouvons parler la même langue, passons le mot!

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Queen Elizabeth II Health Sciences Centre et Université Dalhousie

63rd Annual Scientific Meeting

Calgary, Alberta
July 21–24, 2012

PROGRAM OVERVIEW

FRIDAY JULY 20

1900 – 2100	Registration Open

SATURDAY JULY 21

0730–1700	Registration Open		
0800–1130	Morning Scientific Workshops		
1130–1300	Section Meetings		
1300–1630	Afternoon Scientific Workshops		
1700–1930	Symposium: Patient Safety and Quality Assurance: Case studies, analysis, outcomes		
1930–2200	Residents' Meeting and Dinner		
2000–2200	**Concurrent Special Interest Group Meetings**		
	Biobanking	Informatics	Education

SUNDAY JULY 22

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0800–1130	Morning Scientific Workshops	
1130–1300	Section Meetings	
1300–1630	Afternoon Scientific Workshops	
1700–1745	CAP-ACP Junior Scientist Award Lecture	
1745–1830	CAP-ACP William Boyd Award Lecture	
1830–2000	President's Reception	
2000–2200	**Concurrent Special Interest Group Meetings**	
	Guillermo Quinonez Seminar on the Medical Humanities	International Health

MONDAY JULY 23

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1030–1100	**CAP Sections' Annual General Meetings** Canadian Society of Cytology	Hematopathology Section
1100–1230	Oral Presentations	
1230–1400	Lunch and Exhibit Viewing	
1400–1700	Dr. Cam Coady Slide Seminar: Dermatopathology	
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0800–1030	**Concurrent Symposia** Anatomic Pathology		Pediatric and Perinatal
1130–1200	CAP-ACP Anatomic Pathology Section Annual General Meeting		
1200–1300	CAP-ACP Annual General Meeting Luncheon		
1300–1330	MOC Educational Event		
1400–1700	**Concurrent Symposia** Forensic Pathology	Advanced Diagnostics	Neuropathology
1700–1830	Workshop on Media Relations		Exit Competencies in Pathology and Laboratory Medicine for Canadian Medical Graduates
1900–2200	Gala Banquet and Award Presentations		

SCIENTIFIC WORKSHOPS

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1300 – 1630 ***Afternoon***	W201: Reactive Hematolymphoid Disorders that Mimic Neoplastic Lesions: To Be or Not To Be a Lymphoma W202: The Inside-Out of EUS-FNA W203: Contemporary Issues in the Diagnosis and Management of Breast Disease W204: Perinatal Pathology Made Easy: Placental and Fetal Findings in Adverse Pregnancy Outcome

SUNDAY JULY 22

0800 – 1130 ***Morning***	W301: Histopathologic Diagnosis of Pre-Invasive Lesions of the Female Genital Tract W302: Practical Approach to Atypical/Malignant Cutaneous Spindle Cell Neoplasms W303: Pearls and Pitfalls in Prostate Pathology W304: What's Wrong with FNA of the Thyroid?

1300 – 1630 ***Afternoon***	W401: Practical Pathology of the Luminal Gastrointestinal Tract W402: Dilemmas in Diagnosis and Classification of Myelodysplastic Syndromes W403: Molecular Pathology: Basic Principles and Beyond W404: A Modern Approach to the Diagnosis, Staging and Reporting of Kidney Tumors W405: Mesenchymal Tumors of the Female Genital Tract

Pathological Reporting of Colorectal Polyps: Pan-Canadian Consensus Guidelines

David K. Driman, MBChB, FRCPC, Victoria A. Marcus, MD, FRCPC, Robert J. Hilsden, MD, PhD, FRCPC, David A. Owen, MB, FRCPC

ABSTRACT

Colorectal cancer (CRC) screening programs are in effect in all Canadian provinces, and rely on an accurate diagnosis of CRC precursor lesions. A pan-Canadian consensus process was used to create a set of standardized guidelines for the reporting of polyps that is applicable to all jurisdictions in Canada. These guidelines provide a practical approach to reporting colorectal polyps. In addition, technical aspects in both the endoscopy suite and pathology department, as well as management implications, are discussed.

RÉSUMÉ

Toutes les provinces canadiennes se sont dotées d'un programme de dépistage du cancer colorectal; le diagnostic exact des adénomes précurseurs de la maladie en constitue l'élément capital. Un groupe d'experts canadiens en est venu à un consensus qui se reflète dans des lignes directrices uniformes de classification des polypes applicables dans l'ensemble du pays. Ces lignes directrices balisent le compte rendu d'examen des polypes colorectaux. Elles abordent en outre des aspects techniques relevant de l'endoscopie ou de la pathologie ainsi que la modulation de la prise en charge en fonction des résultats.

As of late 2010, colorectal cancer (CRC) screening programs had been introduced in all Canadian provinces. This has led to enhanced opportunities for the detection and management of patients with precursor lesions, as screening programs allow the use of formal guidelines, quality standards, and audits.

An important role of screening programs is to detect CRC precursor lesions, primarily adenomas and serrated polyps, and thereby identify patients at increased risk for the development of CRC. The management of patients within these programs depends on an accurate diagnosis of colorectal polyps. The use of a standardized set of diagnostic terms by pathologists from all jurisdictions in Canada would enhance the quality of diagnosis and would facilitate subsequent national quality audits. Furthermore, a set of uniformly applied diagnostic standards would be helpful, given that some CRC precursor lesions may be difficult to diagnose and their natural history and clinical implications are not yet fully elucidated.

With this background, a meeting was held in Fredericton,

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This article has been peer reviewed.

Competing interests: None declared

Table 1. Classification of Adenomatous and Serrated Polyps*

Category	Polyp Type	Qualification Regarding Dysplasia
Conventional adenomas	Tubular adenoma	± high-grade dysplasia/invasive adenocarcinoma
	Tubulovillous adenoma	
	Villous adenoma	
Serrated adenomas	Sessile serrated adenoma/polyp	± dysplasia (low-/high-grade)
	Traditional serrated adenoma	± high-grade dysplasia
	Serrated polyp, unclassified	
Hyperplastic polyps		

*Recommended classification system for adenomatous and serrated polyps. Morphological defining features are discussed in the text.

New Brunswick, in September 2010, to initiate the process of reaching a pan-Canadian consensus on the reporting of colorectal polyps. Invitations were sent by the Canadian Partnership Against Cancer (CPAC) through the CRC Screening Network; attendees included pathologists, gastroenterologists, and members of CPAC. Following this meeting, subsequent e-mail discussions, and a teleconference/webinar, a consensus was reached, and it is reported herein. The participants are listed in Appendix 1.

This report presents the consensus group's diagnostic guidelines for adenomatous polyps and serrated polyps (Table 1); other CRC precursors are less common and beyond the scope of this publication. The report aims to offer practical guidelines for pathological diagnosis. Technical issues in both the endoscopy suite and pathology department are also addressed. Lastly, management and surveillance implications are discussed.

Classification of Adenomatous and Serrated Polyps

All conventional adenomas (tubular, tubulovillous, and villous) have, by definition, at least low-grade dysplasia (LGD). Pathologists must report whether there is associated high-grade dysplasia (HGD) and/or invasive adenocarcinoma. With narrative reporting, the appendix *negative for high-grade dysplasia and malignancy* is preferred over *with low-grade dysplasia* to avoid potential confusion and overtreatment by physicians who may not be aware that all adenomas have at least LGD.

In the literature and among members of this group, there was no consensus on the best terminology for sessile serrated lesions. While *sessile serrated adenoma* (SSA) is the preferred term, owing to its growing acceptance in clinical practice and its more widespread use in the literature, *sessile serrated polyp* (SSP) is an acceptable alternative. We note that recent European guidelines have suggested *sessile serrated lesion* as the preferred term.[1] In this manuscript, the abbreviation SSA will be used to include both sessile serrated adenoma and sessile serrated polyp. The term *serrated polyp, unclassified* is reserved for those serrated polyps with features indeterminate between one type and another, for example, between hyperplastic polyp and SSA, or between SSA and traditional serrated adenoma (TSA).

Both SSAs and TSAs may be associated with dysplastic features that are beyond the definitional features of each lesion; such polyps are also referred to as "advanced" SSAs or "advanced" TSAs because the acquisition of such dysplastic features is a morphological indicator that the polyp is advancing toward malignant transformation. There is no consensus in the literature around the best terminology for such lesions.[2] Snover, in a recent review article, advocates the term *SSA with cytological dysplasia* for those SSAs that contain frankly recognizable dysplasia of the type morphologically associated with conventional adenomas.[3] He prefers "cytological" to "conventional" dysplasia because, at a molecular level, these advanced SSAs show microsatellite instability rather than the molecular changes associated with conventional adenomas. For the more unusual advanced TSAs that have recognizable areas of conventional dysplasia, Snover advocates use of the term *TSA with conventional dysplasia*. The molecular features of advanced TSAs are not well characterized.

Our recommendation is that for all SSAs, the pathologist should assess whether morphologically recognizable dysplasia of the type seen in conventional adenomas is present. This should be reported as *negative for dysplasia* or *with dysplasia*. Use of alternative terms such as *conventional*

dysplasia or *cytological dysplasia* is acceptable but not recommended. Since all TSAs have some degree of conventional dysplasia, we recommend that the presence or absence of HGD should be reported, as for conventional adenomas. Note that lesions that have been previously referred to as "mixed SSA – tubular adenoma" are, in most cases, SSAs with dysplasia.

We also recommend that for any sessile serrated polyp in which there is associated dysplasia, a comment should be included in the report to address the clinical significance of the diagnosis. The following is an example of such a comment, which could be modified to suit circumstances: *Sessile serrated adenomas with dysplasia are considered to be advanced lesions that have an increased propensity to transform to adenocarcinoma. Complete endoscopic removal is recommended. If complete endoscopic removal cannot be achieved, short-term re-endoscopy and biopsy, or surgical resection should be considered.*

Adenomatous Polyps

General Features

Conventional adenomas are polyps composed of dysplastic epithelium. Adenomas may be pedunculated, sessile, flat, or depressed. Key features to report include the amount of villous morphology (villosity) present (i.e., tubular versus tubulovillous versus villous), the presence or absence of HGD or malignancy, and, in some examples, the status of the polyp margin, as these features bear on subsequent surveillance intervals or the need for resection. For example, patients with "high-risk" adenomas (a term used in screening programs for tubulovillous or villous adenomas or any adenoma with HGD or ≥10 mm in size) have shorter recommended surveillance intervals than do patients with non-high-risk adenomas.[4] Polyp size can be obtained from gross measurements, but the endoscopically assessed size may be more reliable.

Assessment of Villosity

The designation of adenomas as tubular, tubulovillous, or villous is based on the relative proportions of tubular and villous components present. Polyps in which less than 20–25% of the polyp is villous are classified as tubular, while those in which greater than 75–80% is villous are classified as villous; all others are tubulovillous. This assessment is subjective, and criteria can only be used reliably in polypectomy and complete resection specimens or when there are tissue fragments large enough to assess the various proportions present. Use of the term *at least tubulovillous* is recommended when the polyp is known to be large and at least one villus is present in a biopsy that is small or fragmented.

Three different types of villi may be identified in adenomas: classical, palmate, and foreshortened.[5] Classical villi are long, slender, upgrowths with thin stromal cores, little branching, usually parallel sides, and sometimes bulbous tips; they often appear to extend down to muscularis mucosae. Palmate villi are broader, branching, and leaf-like; there may be tubular glands at the base or within the stromal cores of the villi. Foreshortened villi are slender non-branching outgrowths with thin stromal cores that clearly protrude beyond the overall surface contour of an otherwise well-developed tubular lesion.

It may be difficult to distinguish "true" villi from exaggerated, axially sectioned crypts. In general, it is better to err on the side of under-diagnosis of villous change, especially in small (<1 cm) adenomas.

Grading of Dysplasia and Terminology of Dysplasia

In the gastrointestinal tract, a two-tiered grading system is used for assessing the degree of dysplasia, LGD and HGD. The terms *carcinoma in-situ* and *intraepithelial carcinoma* are not used, with *HGD* being used instead. Conventional adenomas have by definition at least LGD (Figure 1A).

The diagnosis of HGD is *based primarily on architectural features, supplemented by appropriate cytology*. HGD can often be identified at low power as the architecture appears complex and the epithelium lining the crypts looks blue, disorganized, and "dirty." The abnormal architecture includes cribriform formations with "back to back" glands, prominent glandular budding, and intraluminal papillary tufting (see Figure 1B, C, and D). Glandular crowding alone is not a feature of HGD.

These architectural features are usually accompanied by cytological features, such as a loss of cell polarity; nuclear stratification through the entire thickness of the epithelium; markedly enlarged nuclei, often with open, dispersed

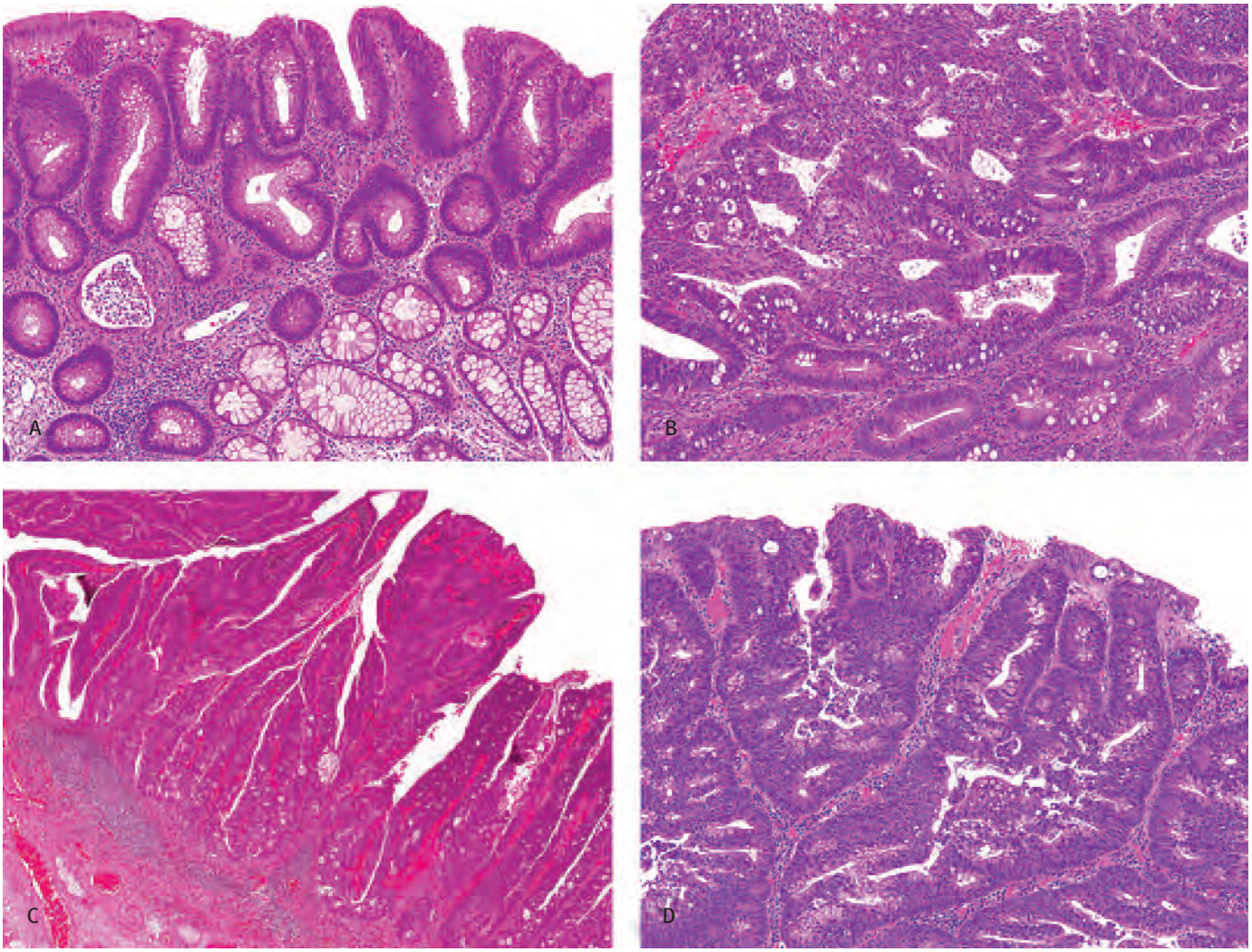

Figure 1. *A*, Adenoma with low-grade dysplasia. *B–D*, Adenomas with high-grade dysplasia; there is architectural complexity with cribriform formations. (Hematoxylin and eosin)

chromatin and prominent nucleoli; atypical mitotic figures; dystrophic goblet cells; and prominent apoptosis imparting a dirty appearance.

The following caveats should be considered when diagnosing HGD (Figure 2A and B):

- **Over-reliance on cytological abnormalities:** Cytological abnormalities should not be used alone for the diagnosis of HGD, except when the cytological abnormalities are particularly marked or, in the case of a small biopsy, when there is insufficient tissue for accurate assessment of architectural abnormalities.
- **Over-calling architectural complexity:** There is often a minor degree of budding in tubular adenomas that does not constitute HGD.
- **Over-calling surface changes:** Surface changes in small adenomas, such as a loss of nuclear polarity and nuclear stratification, without architectural complexity should not be over-interpreted; these usually stem from trauma, erosion, or prolapse.
- **Insufficient extent of abnormalities:** In order to diagnose HGD, typical abnormalities should usually involve more than two crypts.

According to World Health Organization recommendations, the term *HGD* should be used instead of *intramucosal carcinoma* for adenomatous polyps in which there is mucosal invasion, that is, invasion of the lamina propria

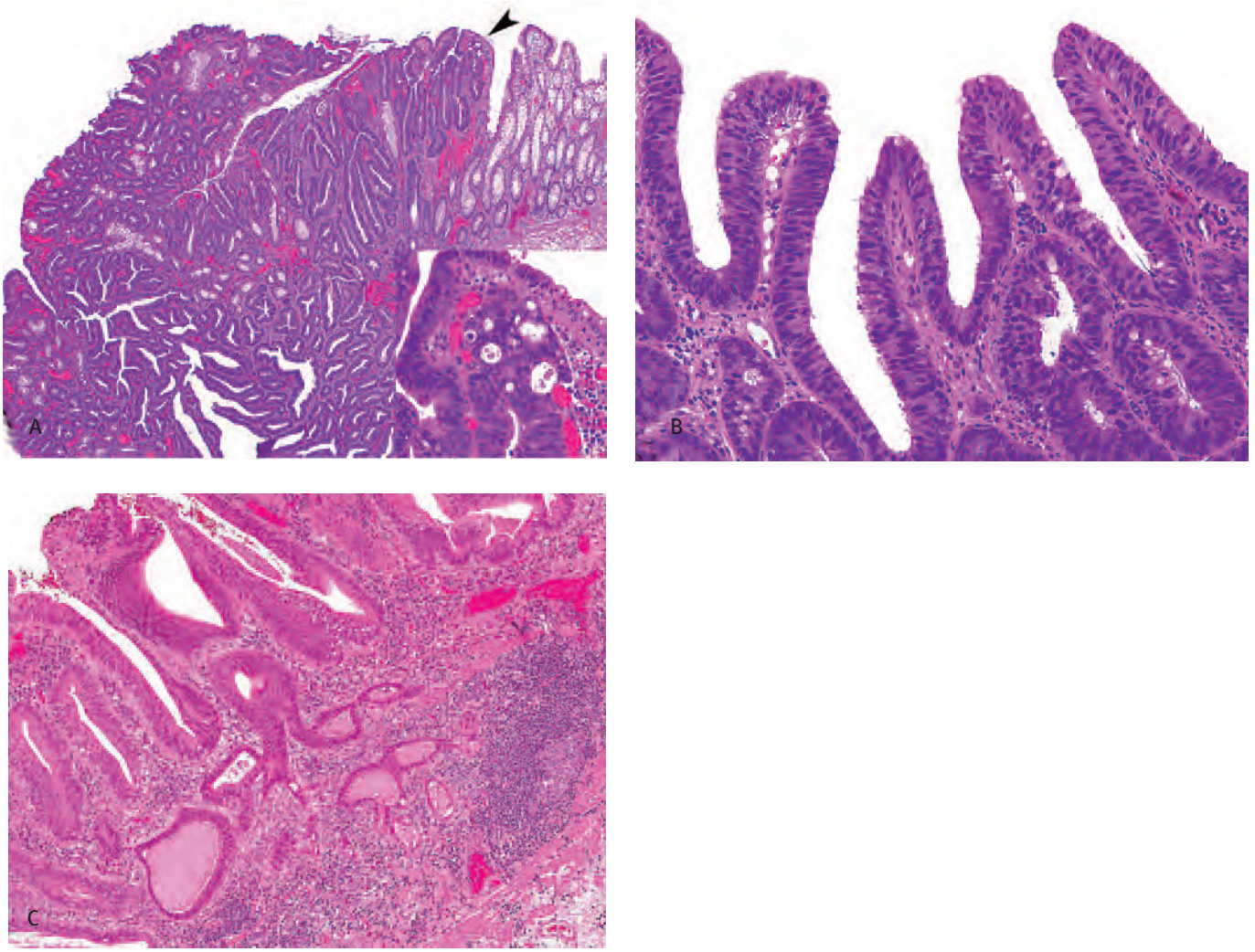

Figure 2. *A*, Adenoma with focal cribriform architecture (*arrowhead* and *inset*); this is not sufficient for a diagnosis of high-grade dysplasia. *B*, Adenoma with nuclear stratification through the full thickness of the epithelium but without architectural atypia and a loss of nuclear polarity; this does not constitute high-grade dysplasia. *C*, Adenoma with lamina propria invasion; this is typically reported as high-grade dysplasia rather than intramucosal carcinoma. (Hematoxylin and eosin)

with or without muscularis mucosae (see Figure 2C).The rationale for this is that mucosal invasion alone (i.e., without submucosal invasion) is associated with a negligible risk of malignant biological behaviour as indicated by a spread to lymph nodes; therefore, in the majority of cases, these lesions do not require further surgery. In cases where there is mucosal invasion, it is recommended that a comment be inserted to explain the use of the term *HGD* and to expand on the findings and significance.

Malignant Polyps

Malignant polyps are polyps with invasive adenocarcinoma, defined as invasion through the muscularis mucosae into the submucosa (pT1). This definition excludes polyps in which there is invasion into the lamina propria or muscularis mucosae (reported as HGD). In almost all malignant polyps, submucosal invasion is accompanied by a desmoplastic stromal reaction, whereas mucosal invasion is not typically associated with stromal desmoplasia.

The following pathological features must be reported in malignant polyps as they predict adverse outcome, that is, residual carcinoma or lymph node spread at subsequent colectomy or in 5-year clinical follow-up[6]:

- The presence or absence of any amount of poorly differentiated adenocarcinoma
- The presence or absence of angiolymphatic invasion
- The distance of invasive adenocarcinoma from margin

of resection, with a distance of 1 mm or less considered to represent a positive margin

The following features are optional for reporting:

- **The presence or absence of tumour budding:** This refers to the presence of single infiltrating tumour cells or small groups of tumour cells at the invasive front of the tumour. While budding is an adverse prognostic sign, diagnostic criteria vary and there are issues with reproducibility of its assessment.[7,8]
- **Haggitt and Kikuchi levels:** Haggitt levels apply to pedunculated polyps and refer to the depth of invasion as follows: level 1 – carcinoma confined to head of polyp; level 2 – carcinoma down to the neck of the polyp (junction of head and stalk); level 3 – carcinoma into the stalk; and level 4 – carcinoma into the submucosa at the level of the adjacent bowel wall.[9] Kikuchi levels apply to sessile polyps and refer to the depth of invasion within the submucosa, that is, superficial, middle, or deep thirds, and this corresponds to the frequency of nodal metastases (2%, 8%, and 23%, respectively).[10] Both Haggitt and Kikuchi levels are difficult to apply in practice: the assessment of Haggitt levels requires a perfectly orientated specimen, while the assessment of Kikuchi levels requires the presence of muscularis propria.

Invasive adenocarcinoma in an adenomatous polyp must be distinguished from pseudoinvasion or misplaced/herniated adenomatous glands in the submucosa. This is frequently seen in pedunculated polyps in the sigmoid colon because of the tendency for polyps in this location to undergo torsion. There are several clues to the presence of pseudoinvasion rather than true invasion: The submucosal glands are surrounded by lamina propria and do not have cytoarchitectural features of malignancy. There is hemorrhage and hemosiderin in the surrounding submucosa and no desmoplastic stroma. Admixed normal glands may also be present in the submucosa, and there may be acellular mucin pools. Ischemic changes (granulation tissue, erosions, exudate) are often present at the surface of the polyp due to torsion. Finally, invasive adenocarcinoma is usually associated with HGD elsewhere in the polyp; if this is absent, malignancy should be diagnosed with caution.

Reporting Completeness of Excision

Because of the implications for post-polypectomy management, a statement about completeness of excision is required for all malignant polyps (polyps with invasive adenocarcinoma) with the measured distance of the malignant component from the margin stated. For all polyps with HGD, it should be stated specifically whether the dysplasia is present or absent at the margin. In many cases, this will not be assessable due to fragmentation, and this should be stated in the report.

A statement about completeness of excision is optional for adenomas without HGD and is generally not recommended. Statements such as *may not be completely excised* or *completeness of excision cannot be assessed* can lead to confusion among treating physicians and unnecessary re-referrals in situations where the endoscopist is not attempting to obtain a margin of normal tissue and is using electrocautery to destroy any residual lesional tissue.

Serrated Polyps

Hyperplastic Polyps

Hyperplastic polyps are most frequently found in the distal colon and rectum. Hyperplastic polyps have serrations that are prominent in the luminal halves of crypts, with crypt bases that are straight and narrow. Because the normal crypt proliferative zone is in the lower third to one half of the crypts, lining cells in this location have a more immature appearance with mitoses. Cells in the upper half of the crypts show maturation. Hyperplastic polyps may be subdivided based on their mucin characteristics; although, at the present time, routine diagnostic subclassification of hyperplastic polyps is not recommended. Microvesicular hyperplastic polyps have cells with predominantly microvesicular mucin, goblet cell–rich hyperplastic polyps have their mucin localized in goblet cells with little microvesicular mucin, and mucin-poor hyperplastic polyps have little to no mucin (Figure 3A and B). Microvesicular hyperplastic polyps are found throughout the colon, whereas goblet cell–rich hyperplastic polyps are found almost exclusively in the left colon. Mucin-poor

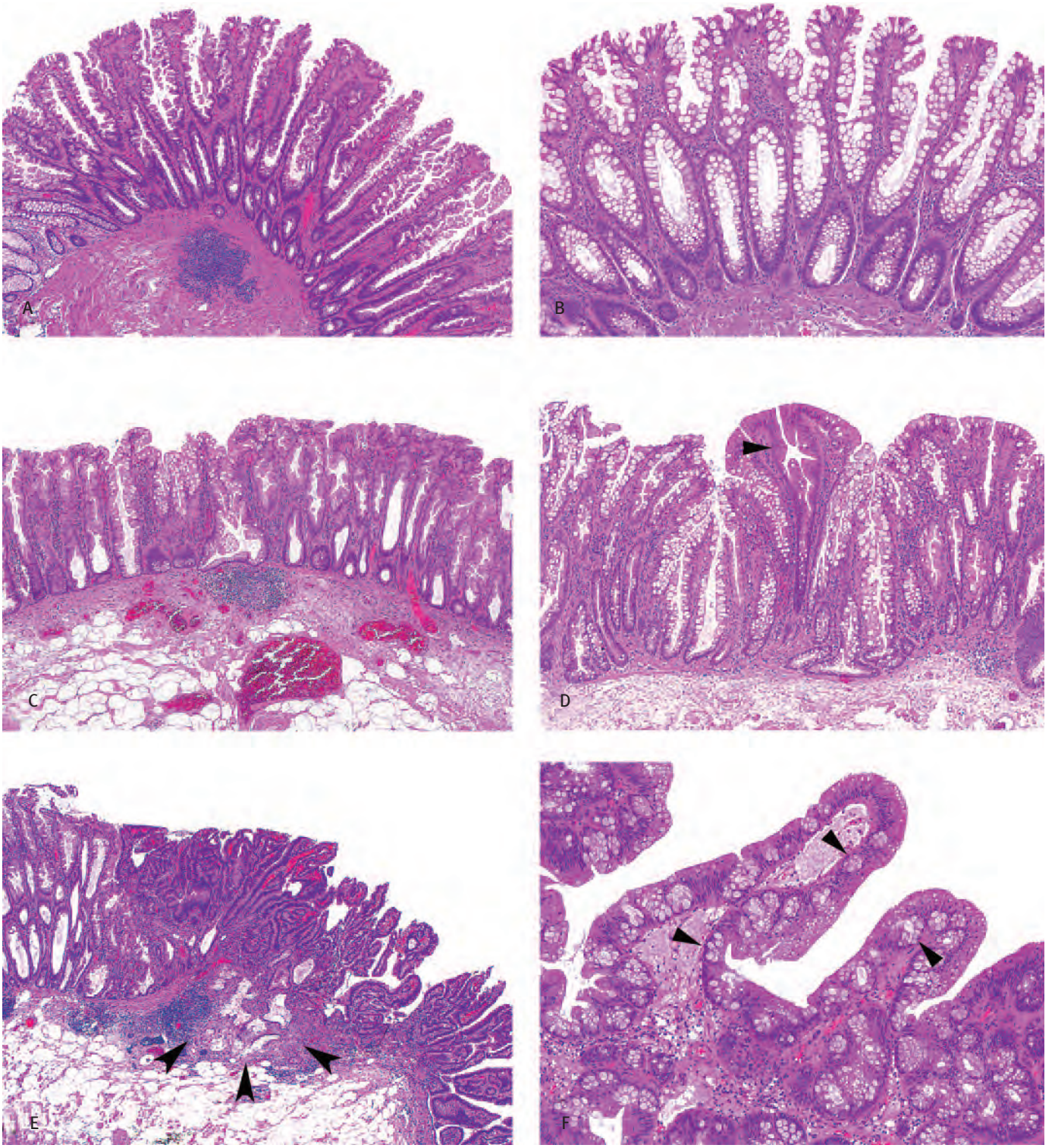

Figure 3. *A*, Hyperplastic polyp (microvesicular type). *B*, Hyperplastic polyp (goblet cell type). *C*, Sessile serrated adenoma with submucosal fat, which is commonly seen in association with these polyps. *D*, Sessile serrated adenoma with a focus with pencillate cells and rigid serrations *(arrowhead)*, changes seen more extensively in traditional serrated adenomas. *E*, Sessile serrated adenoma with dysplasia and invasive adenocarcinoma *(arrowheads)*. *F*, Traditional serrated adenoma with innumerable budded crypt foci *(arrowheads)* . (Hematoxylin and eosin)

hyperplastic polyps have not been well studied.

Sessile Serrated Adenomas/Polyps

SSAs occur throughout the colorectum but are more common on the right side, where they outnumber hyperplastic polyps.[11] They are often larger than 10 mm and may be difficult to see at endoscopy because of their tendency to be flat, ill-defined lesions on the crests of mucosal folds; their colour is similar to the background mucosa.[12] SSAs are characterized by both architectural and cytological abnormalities.[2,3] Architectural abnormalities predominate and are the most recognizable feature of these polyps, particularly at low magnification. In contrast to hyperplastic polyps, there are deep crypt abnormalities with exaggerated deep crypt serration, abnormally located, differentiated cells (goblet or gastric in type), horizontally spreading boot- or anchor-shaped crypt bases or dilated crypt bases. Upper crypt abnormalities are present and comprise enlarged vesicular nuclei with prominent nucleoli and upper crypt mitoses. Submucosal fat is often present underneath SSAs, and the presence thereof does not imply an additional diagnosis of lipoma (see Figure 3C).

When examining SSAs, pathologists must exclude dysplasia, which is typically in the form of conventional dysplasia, that is, resembling the dysplasia found in conventional adenomatous polyps. The presence of dysplasia in an SSA is an indication that the lesion is advanced, with an increased, and probably more rapid propensity to develop into adenocarcinoma (see Figure 3D and E).[13–15]

Traditional Serrated Adenomas

TSAs are the least well-studied member of the serrated polyp group. These polyps are most apt to be misdiagnosed as tubulovillous or villous adenomas as TSAs are protuberant rather than sessile and usually have recognizable villi or papillary projections, with prominent and rigid serrations. TSAs typically contain slender cells with eosinophilic cytoplasm that have thin, elongated "pencillate" nuclei; the nuclei are often centrally located within the cell, and mitoses are rare in these cells (see Figure 3D). A defining feature is the presence of ectopic budding crypts that appear to bud into the underlying lamina propria (see Figure 3F).[16] All TSAs have some degree of conventional dysplasia. Advanced TSAs are those lesions that have a greater degree of dysplasia, akin to HGD in conventional adenomas. We recommend that pathologists report the presence or absence of HGD in all TSAs.

Specimen Handling and Processing

Endoscopy Suite

In the endoscopy suite, the following should be observed:

- Polyps from different locations in the colorectum should be submitted in separate containers and labelled as to their site of origin.
- Multiple small polyps from the same location can be submitted in the same specimen container.
- The endoscopist should indicate on the requisition form whether the submitted specimen represents a biopsy of a polyp or a polypectomy specimen.

Pathology Laboratory

In the pathology laboratory, the following information should be recorded:

- The number and size of polyps or tissue fragments (or range in size, if multiple)
- The presence or absence of a stalk in intact polyps
- The length and diameter of stalk, if present

Tissue Sectioning and Processing

It is important that polyps be properly fixed prior to sectioning, in order that the centre of the polyp, which usually harbours the area most important for assessment, is well processed; there should be no reluctance to allow polyps to fix overnight before sectioning. Polyps should be submitted in their entirety and must be sectioned to demonstrate the polyp stalk in the most optimal manner. Ink should be applied to the base of the stalk. If a stalk is not present, and the polyp is large enough to be sectioned (see below), pale tissue at the base of the polyp should be sought and ink applied to this area. The method of sectioning depends on the diameter of the head of the polyp, not the size of the stalk, as indicated in Table 2.

If biopsies of a polyp fail to show any evidence of a lesion in the standard two or three initial sections, consideration

Table 2. Guidelines for Gross Sectioning of Colorectal Polyps

Diameter of Polyp Head	Sectioning Protocol	Levels (50 μM)
<0.4 cm	No sectioning required	2–3
0.4–0.8 cm	Bisect and place in 1 cassette	2–3
0.9–1.2 cm	Trisect by shaving two sides off central section with stalk; place central section in separate cassette	2–3 (on central section)
>1.2 cm	Cut as many sections as appropriate to submit the central stalk area and submit in separate cassettes	2–3 (on stalk sections)

should be given to cutting deeper levels, as small tubular adenomas can be detected in deeper levels in around 10% of cases.[17,18]

Aside from endoscopically derived specimens, the pathologist may also receive surgically resected transanal excisions of rectal polyps. These specimens should be orientated and pinned to avoid curling of the edges with fixation. Ink should be placed on all the resection margins: deep (radial), proximal, distal, and lateral, if the transanal resection was non-circumferential. Perpendicular sections of all margins should be taken. The specimen should be submitted in its entirety in a manner that allows for the completeness of excision to be documented.

Management and Surveillance

This section provides a summary of the general management and surveillance guidelines for adenomas and serrated polyps. All polyps, no matter the type, should be completely removed endoscopically. If this cannot be achieved at the first endoscopy, a repeat endoscopy within 2–6 months, depending on patient factors and endoscopic findings, should be undertaken to biopsy the lesion further and to attempt to remove it. The exception to this is the presence of multiple small hyperplastic-appearing polyps in the distal sigmoid/rectum; these can be sampled, but the removal of all is usually not feasible. Patients with rectosigmoid hyperplastic polyps do not require further surveillance, but endoscopists should be aware of the potential pathological misclassification of hyperplastic polyps and SSAs.[19] Follow-up is recommended if there are more than three hyperplastic polyps proximal to the rectosigmoid colon or if any polyp larger than 1 cm is diagnosed as a hyperplastic polyp.

Patients with conventional tubular adenomas should undergo endoscopy again, no sooner than 5 years after the initial endoscopy if there are no more than two tubular adenomas without HGD and neither is larger than 1 cm.[19] Re-endoscopy in 3 years is recommended if there are three or more adenomas or if any adenoma is at least 1 cm, is tubulovillous or villous, or has HGD.

There are currently no established clinical practice guidelines on the management of SSAs and TSAs as their natural history and associated risk for future advanced polyps or cancers are not fully elucidated. Therefore, recommendations are based on expert opinion. Patients with SSAs or TSAs should undergo endoscopy again in 3–5 years' time if there are no more than two polyps and neither is larger than 1 cm.[20–22] Re-endoscopy in 3 years is recommended if there are three or more polyps or if any polyp is at least 1 cm. Advanced forms of serrated polyps, particularly SSAs with dysplasia, should be managed particularly carefully because of their more frequent association with malignancy.

Conclusion

In this document, we have provided guidelines for the reporting of adenomas and serrated polyps. The standardization of terminology has become particularly important with the advent of CRC screening programs across Canada and the need for uniform understanding of the clinical implications of these lesions by pathologists, gastroenterologists, surgeons, and oncologists. We recognize that these guidelines will, by necessity, require updating over time as new data accumulate on the pathology and clinical implications of many of these lesions.

Acknowledgement

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Appendix 1. Members of the Pan-Canadian Consensus Group

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Members of Canadian Partnership Against Cancer staff who assisted with this initiative were Susan Fekete, Verna Mai, and Catherine Hunter.

The Rare Rapunzel Bezoar

Etienne Mahe, BSC, MD, Chad Wherry, MD, Jorge Arredondo Marin, MD

ABSTRACT

A mass removed from the stomach of a 3-year-old boy was found to be a trichobezoar. The different forms of bezoar are briefly reviewed.

RÉSUMÉ

Présentation du cas d'un garçon de trois ans opéré pour un trichobézoard à l'estomac. L'article passe en revue brièvement les formes de bézoard.

Case Description

A 3-year-old boy with developmental delay presented to the emergency department complaining of epigastric fullness and vomiting immediately after each meal. The vomitus in each episode consisted of the food most recently consumed prior to vomiting, and the problem had increased over the 2 weeks preceding presentation. Of significant note, the patient's mother confirmed a history of consumption of pieces of carpet in the weeks leading up to his presentation. When pressed as to why he might be behaving this way, his parents could offer no explanation but reported that they had been unable to prevent it. The patient himself could not provide any additional significant history.

The patient's initial examination and flat-plate abdominal imaging raised the possibility of a mass in the stomach (Figure 1). The patient was referred to our centre for further investigation, and a follow-through examination of the small bowel was attempted. Although this study was not technically ideal, the findings did suggest a large mass in the stomach lumen, consistent with a bezoar (Figure 2). A surgical consultation was immediately arranged, and subsequent laparotomy revealed a large Rapunzel bezoar (Figures 3 and 4). This was sent to the Pathology Department with a request for determination of the predominant constituents of the mass.

Discussion

The term *bezoar* refers to any concretion formed in the stomach, and in many instances, the specific type of bezoar will relate to the underlying etiology.[1] The more common bezoars, for instance, the trichobezoars, are most frequently associated with psychiatric conditions, such as trichotillomania, in which consumption of hair leads to gastric

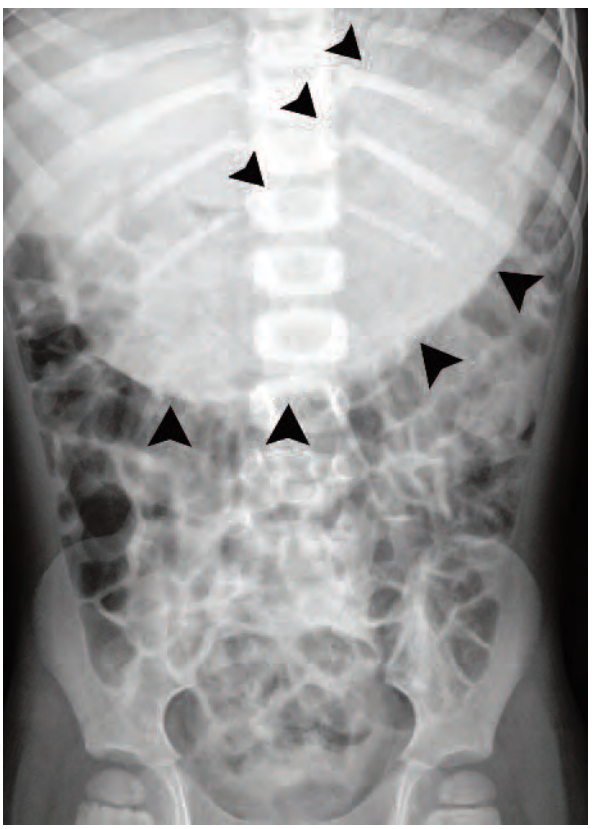

Figure 1. Initial flat-plate abdominal radiograph demonstrating gas-filled small and large bowel loops but opacification of the gastric silhouette *(arrowheads)*.

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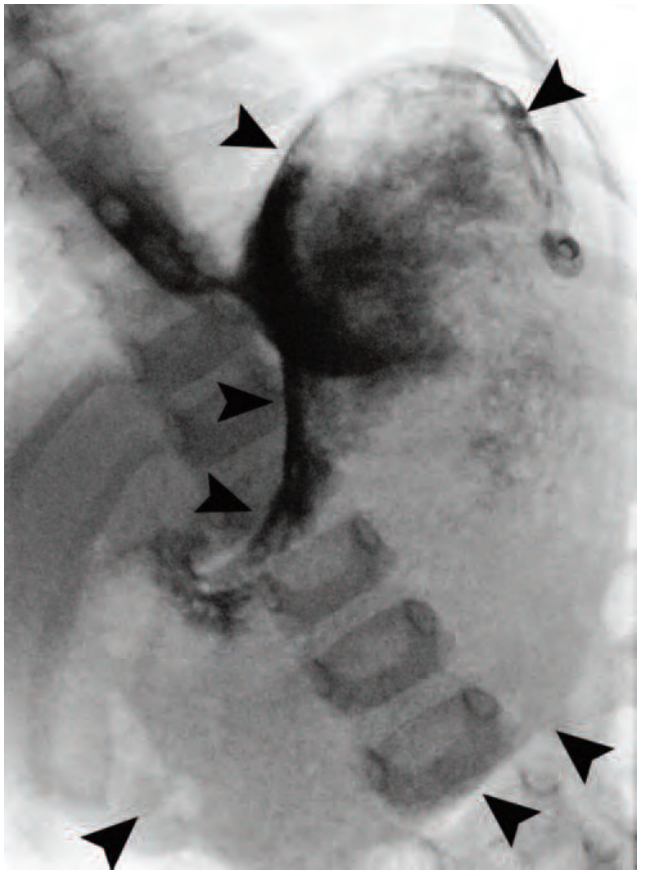

Figure 2. Small bowel follow-through demonstrating gastric filling defect *(arrowheads)*.

Figure 3. Gastric bezoar specimen. Note the outline of the stomach and the long tail extending into proximal small bowel (*short arrow* denotes contour of greater curvature; *long arrow* denotes tail extending into small bowel).

accumulation. Other forms of bezoars include infectious bezoars (in which, for example, mats of *Candida albicans* may be the culprit), postgastrectomy bezoars (in which inadequately masticated foodstuff becomes impacted in the stomach with inherently reduced mechanical digestive capacity), as well as lactobezoars (in which milk protein

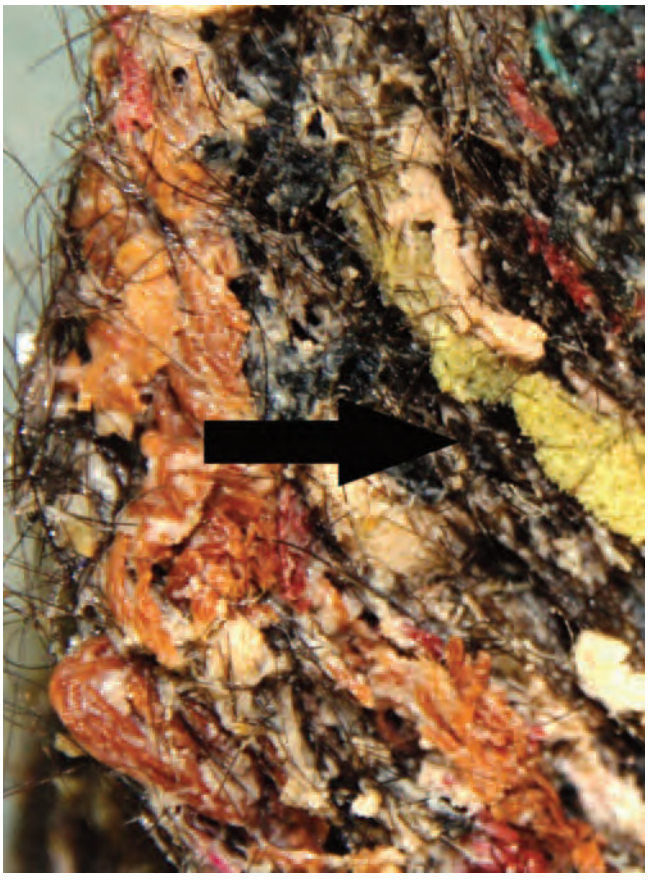

Figure 4. Close-up of a cut made into the specimen demonstrating carpet fibres and pieces of carpet underlay material *(arrow)*.

solidifies in the stomach).[1]

The rare Rapunzel bezoars are the *sine qua non* of the so-called Rapunzel syndrome.[2] These patients have extremely large trichobezoars with tails extending into the small bowel and an associated element of obstruction.[2] This rare condition is named after the fairy-tale character Rapunzel, known for her extremely long hair.[2] Most patients present with abdominal pain, nausea, vomiting, and symptoms of obstruction, frequently in association with a psychiatric condition.[2] Treatment generally requires surgical removal of the extremely large and immobile trichobezoar.[2]

While the case cited above is not a classic instance of Rapunzel syndrome, since the bezoar does not consist *entirely* of hair, the contents of the bezoar were of similar structure and produced a compatible clinical picture.

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Review of Peritoneal Washings: Diagnostic Challenges and Pitfalls

Michele M. Weir, MD, FRCP

ABSTRACT

The interpretative challenges commonly encountered in the cytological evaluation of peritoneal washings are reviewed. The cytological distinction of reactive mesothelial cells from endometriosis, endosalpingiosis, and various carcinomas of the female genital tract is discussed, with summaries of the helpful clues to correct diagnosis.

RÉSUMÉ

L'article passe en revue les difficultés courantes que pose l'interprétation des résultats de la cytologie péritonéale par lavage. Il aborde la distinction cytologique entre les cellules mésothéliales d'aspect réactionnel et l'endométriose, l'endosalpingiose et divers carcinomes des organes génitaux féminins et propose un résumé d'indications utiles pour poser un diagnostic précis.

Peritoneal washing samples first gained value as diagnostic and prognostic indicators in the 1960s and 1970s.[1–3] Subsequently, peritoneal washings have been performed for gynecological oncologic surgeries to assist in the detection of peritoneal neoplasia, since intraoperative visual inspection of the peritoneum may not detect all peritoneal disease.[2–4] The main uses for peritoneal washings in gynecologic oncology have been for (1) the detection of occult, recurrent, or persistent tumours, (2) staging, and (3) prognostic information.[1–3] Although initially recognized as a simple and effective tool for gynecological oncologic staging, the use of peritoneal washings continues to evolve with new staging systems, and they seem to play a more limited role in the staging of some gynecological malignancies, such as cervical and endometrial.[3–7] In most patients with a gynecological malignancy, positive peritoneal cytology indicates a poor prognosis and a correspondingly positive peritoneal histological sample.[8] The one exception is serous borderline tumour (SBT) with extra-ovarian implants, which is usually not associated with a poor outcome in most patients, unless there are invasive implants outside the ovary.[8,9]

Morphological examination of peritoneal washings may have lower sensitivity and specificity compared with other cytology samples.[10] The false-negative rate for peritoneal washings may be as high as 20%, while the false-positive rate may reach 4.5%.[2,10] Reasons for this include poor sampling and interpretative challenges. Poor sampling may be the result of infrequent tumour exfoliation or poor distribution of the peritoneal washing fluid within the pelvis and abdomen.[10,11] Interpretative challenges may be due to the under-recognition of a few malignant cells in a sea of benign mesothelial cells, or the misinterpretation of reactive mesothelial cells and other benign entities as malignant.[10,12] The mechanical trauma from the washing procedure results in additional mesothelial morphologies not seen in ascites samples, as well as denudation of fallopian tube epithelium, endometriosis, and endosalpingiosis. The purpose of this

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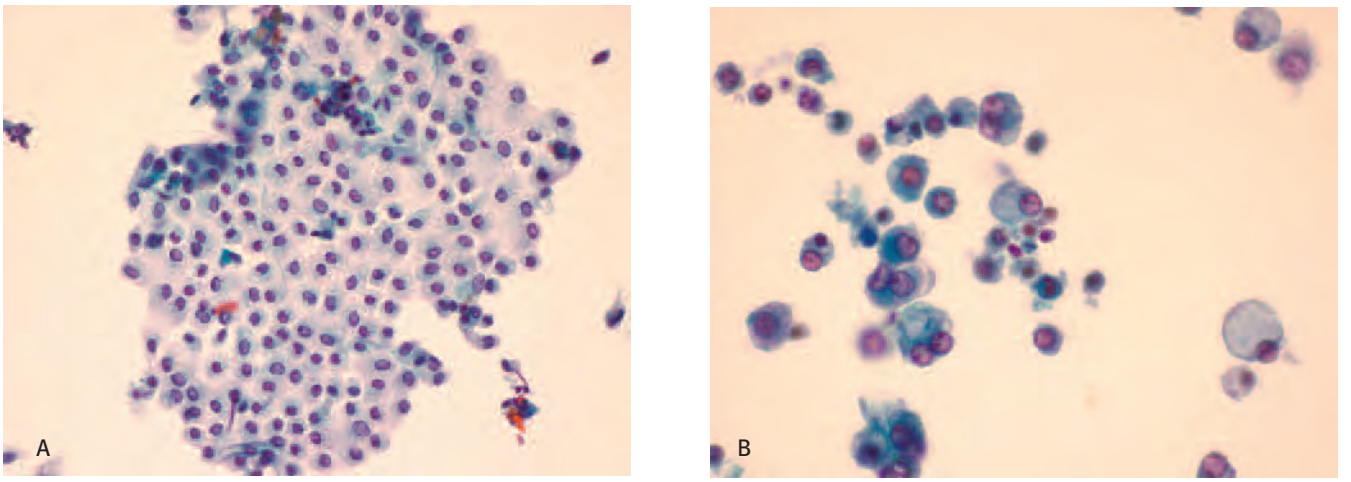

Figure 1. Peritoneal washings with benign mesothelial cells. *A*, Instrumented sheets with bland nuclei and nuclear membrane crenation. *B*, Typical morphology with intercellular windows, cell clasping, fuzzy cell edges with blebs, and reactive nuclei (nucleoli, binucleation, enlargement). (Papanicolaou stain)

review is to focus on the common interpretative pitfalls associated with peritoneal washings and to provide some clues to assist in distinguishing reactive mesothelial cells and other benign entities from selected malignancies.

The False Positives and Diagnostic Challenges

Reactive Mesothelial Cells

The mechanical trauma from peritoneal washings results in additional mesothelial cell morphologies, which are not identified in ascites samples and may result in a false-positive diagnosis. The presence of large flat or folded sheets without intercellular windows and with smooth flat edges may mimic a carcinoma (Figure1A). However, the organized pattern of the nuclei in the sheets and the lack of significant nuclear atypia are clues to their mesothelial nature. Nuclear changes within the cells of instrumented sheets, termed *daisy cells*, are another interpretative pitfall of peritoneal mesothelial cells.[13] Attention to the polarity of the cells, the unusual petal-like appearance of the nuclear contours, and repetitiveness of nuclear crenation are clues to mesothelial recognition.[13]

Other reactive changes within mesothelial cells may be problematic for the interpretation of peritoneal washings. There may be concerning nuclear atypia (enlargement, increased nuclear-to-cytoplasmic [N/C] ratios, prominent nucleoli), cellular features (increased size, vacuoles), and architectural arrangements of hyperplasia (simple papillae, cell balls) that may mimic adenocarcinoma. As well, calcifications may be associated with reactive mesothelial cells, mimicking a papillary serous neoplasm. Morphological clues to adenocarcinoma include a mucin droplet vacuole ("bird's eye" or "bull's eye") with impingement on the nuclear contour, significant coarse chromatin with parachromatin clearing, nuclear membrane irregularity, and abnormal angulated macronucleoli, which may be multiple.[14] Smooth contours of the cell groups with lack of intercellular windows are the typical architectural features of adenocarcinoma. However, with higher-grade adenocarcinoma, cellular dyshesion usually results in irregular clusters and windows, mimicking mesothelial morphology.[14,15] Other typical architectural features of adenocarcinoma include vacuolated cell clusters, pseudoacinar groups, and large papillary fronds.[16]

Morphological clues to mesothelial cells include cytoplasmic surface fuzziness and blebs, two-toned cytoplasm (denser around the nucleus), multiple intracytoplasmic peripheral vacuoles, and a lack of impingement of single vacuoles on the nuclear contour (see Figure1B and Table 1).[17] The similarities between the reactive atypia of mesothelial cells and the less atypical mesothelial cells in the background span the spectrum of changes, and this may aid in the recognition of reactive atypia.[16] In challenging cases, correlation with a concurrent histological sample may aid in clarifying the ambiguity. However, when necessary for staging purposes, some cases may require immunomarkers to delineate mesothelial versus adenocarcinoma origin.

Finally, treatment effects (from neoadjuvant chemotherapy and/or radiation therapy) may result in significant mesothelial cell atypia that may mimic malignancy. Attention to the degenerative nature of the nuclear

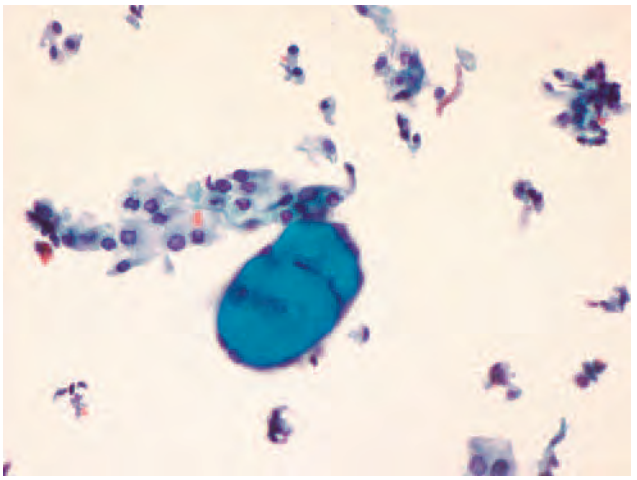

Figure 2. Collagen ball in a peritoneal washing has a central, waxy, dense, three-dimensional core surrounded by flat bland mesothelial cells. (Papanicolaou stain)

Table 1. Diagnostic Clues: Mesothelial Cells

Intercellular windows, irregular group contours
Lack complex branching papillae
Two-toned cytoplasm, surface blebs, and fuzziness
Peripheral small vacuoles or single large vacuole without nuclear impingement
Lack of marked nuclear atypia and overlap
Small nuclei and cells
If reactive, spectrum of nuclear changes

Table 2. Diagnostic Clues: Collagen Ball

Central, waxy, homogenous ball
No complex architecture
Single layer of bland cuboidal cells
Mesothelial immunoprofile

chromatin and glassy nuclear features may help in identifying the atypia related to treatment effects.[18] In some cases, when the nature of the atypia cannot be entirely resolved with a review of the concurrent histology or by immunomarker studies, an indeterminate or inconclusive report may be issued.

Collagen Balls

The collagen ball is an important morphological pitfall in peritoneal washings since it may mimic a mucin-rich adenocarcinoma or a papillary serous neoplasm.[19] Although uncommon in peritoneal fluids (1.6%), the collagen ball has been identified more frequently in pelvic washings (5.8%), which may be due to its postulated site of origin.[19] Wojcik and Naylor proposed that the collagen ball originates from the ovarian surface; its histological correlate is the papillary stromal projection covered by ovarian mesothelium.[19] When recognized by the cytologist in a peritoneal washing, the collagen ball is of no particular significance.[13,19] The classic appearance is a homogenous, globular, waxy green (by Papanicolaou stain) three-dimensional ball covered by a single layer of bland cuboidal cells that show the immunoprofile of mesothelial origin (Figure 2; Table 2).[13,19,20] Morphological features that overlap with papillary serous neoplasm include the smooth contour of the cell ball and the lack of obvious intercellular windows. However, the collagen ball lacks the complex papillary architecture of a papillary serous neoplasm.[13] Sometimes, the central collagen may be mistaken for either mucin, leading to misinterpretation as adenocarcinoma, or calcification, raising the possibility of a papillary serous neoplasm. However, mucin is not as prominent or as well-defined as the central waxy material of the collagen ball. As well, only a simple layer of epithelium accompanies the collagen core.[13]

Endometriosis

Endometriosis is a challenge in peritoneal washings due to its overlapping morphological features with adenocarcinoma and papillary serous neoplasms. Endometrial cells may be difficult to identify in peritoneal washings, and as a result are likely labelled as mesothelial cells in some instances. The combination of hemosiderin-laden macrophages and endometrial epithelial cells is highly specific (96%), albeit not very sensitive (33%), for the diagnosis of endometriosis.[21] Therefore, the presence of hemosiderin-laden macrophages should alert the cytologist to search for endometrial cells.[10,13,20,21]

In abdominal endometriosis, the peritoneal washing may demonstrate two endometrial cell types: the small cuboidal epithelial cell and the rare small spindled stromal cell. The epithelial cells are arranged in simple three-dimensional clusters and sheets, which may be tubular (Figure 3A).[10,21] The cells are tiny and appear crowded due to scant cytoplasm compared with mesothelial cells. As well, there may be intracytoplasmic vacuoles. The endometrial cells have eccentric, round to bean-like nuclei with minimal nuclear atypia (bland fine chromatin, rare nucleoli) in contrast to the significant nuclear atypia of high-grade adenocarcinoma.[10,21] The small cell size, presence of hemosiderin, and lack of complex papillae are clues that distinguish endometriosis from a papillary serous neoplasm

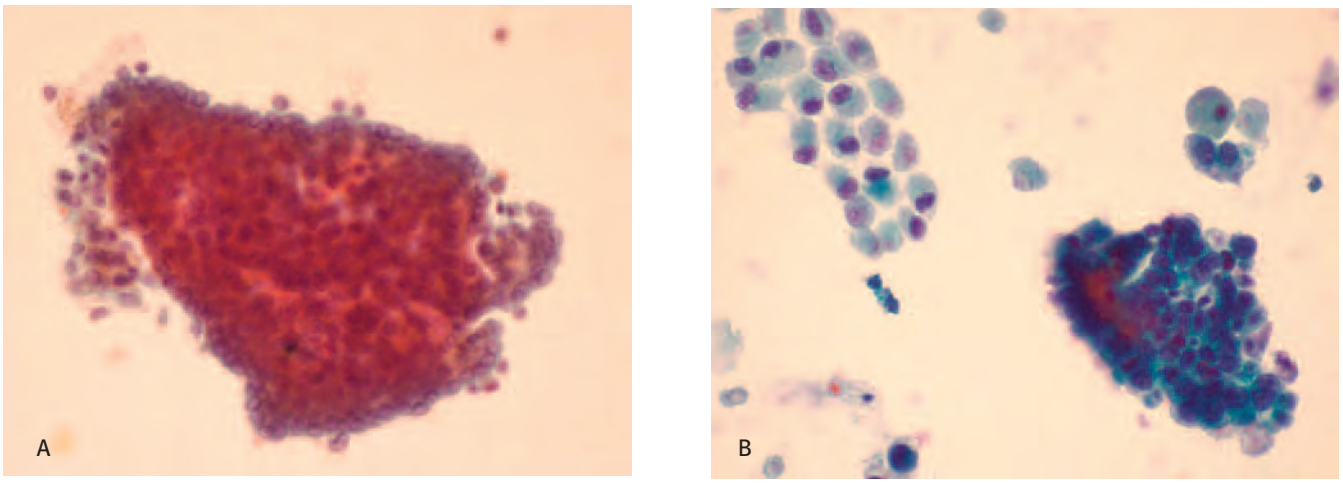

Figure 3. Benign mimics of malignancy in peritoneal washings. *A*, Endometriosis: crowded glandular cells in an organized cohesive group associated with hemosiderin-laden macrophage at top left. *B*, Ciliated epithelium: crowded glandular cells in a simple group arrangement with moderate nuclear atypia. Note the prominent cilia at one edge and background mesothelial cells. (Papanicolaou stain)

Table 3. Diagnostic Clues: Endometriosis

Tubules, sheets, three-dimensional clusters, no papillae
Small crowded cells with high nuclear-to-cytoplasmic ratios
Bland eccentric nuclei
Prominent vacuoles
Hemosiderin

Table 4. Diagnostic Clues: Ciliated Epithelium

Cohesive organized fragments, sheets
Simple non-branching papillae
No or slight atypia
Cilia

(Table 3). The distinction between endometriosis and low-grade endometrial adenocarcinoma is problematic. The presence of nuclear atypia (nucleoli, parachromatin clearing) and dyshesion may help in identifying the latter.[18,22] However, it may be prudent in particularly challenging cases where the clinical scenario and histological samples are not informative to render a differential diagnosis of endometriosis versus low-grade endometrioid adenocarcinoma in the report.

Endosalpingiosis and Tubal Sampling

The vigorous mechanical irrigation from peritoneal washings may result in the presence of ciliated epithelium from the fallopian tubes or peritoneal endosalpingiosis. It is important to distinguish ciliated epithelium from papillary serous neoplasm. Ciliated epithelium is usually cohesive and arranged in tightly organized fragments, sheets, and non-branching simple papillae with cilia (see Figure 3B and Table 4).[10,13,20,23–26] The clue that distinguishes it from papillary serous neoplasm is the presence of simple papillae with no or slight nuclear atypia (smooth contours, fine chromatin, small nucleoli).[10,13,20,23–26] In contrast, papillary serous neoplasm may demonstrate either large complex papillae with architectural disorganization or simple papillae with marked atypia, as seen in the higher grades of serous adenocarcinoma.[10,24] The presence of nuclear molding and nucleoli may suggest neoplasia in some cases.[10] Calcification (psammoma bodies) and cilia may be associated with both ciliated epithelium and papillary serous neoplasm and should not be used as a distinguishing feature for the latter.[10,25,26] A cell block may be particularly helpful for the recognition of cilia and the typical architecture of ciliated epithelium.[10,20,23]

The False Negatives and Diagnostic Challenges

Ovarian Papillary Serous Neoplasms

Peritoneal washings are used for the staging of ovarian borderline and malignant neoplasms in general. A positive peritoneal washing in the absence of positive pelvic or abdominal peritoneal histological samples raises the stage of the ovarian neoplasm to a IC (with one or both ovaries involved) or IIC (with pelvic extension and one or both ovaries involved).[27] For SBT, peritoneal washings only identify the presence of the tumour but cannot be used to determine the need for chemotherapy since it is not possible to distinguish the non-invasive from invasive implants in a cytological sample. For low- and high-grade serous adenocarcinoma (LGSC, HGSC), peritoneal washings may aid in identifying microscopic extra-ovarian disease in some patients, which warrants adjuvant chemotherapy.

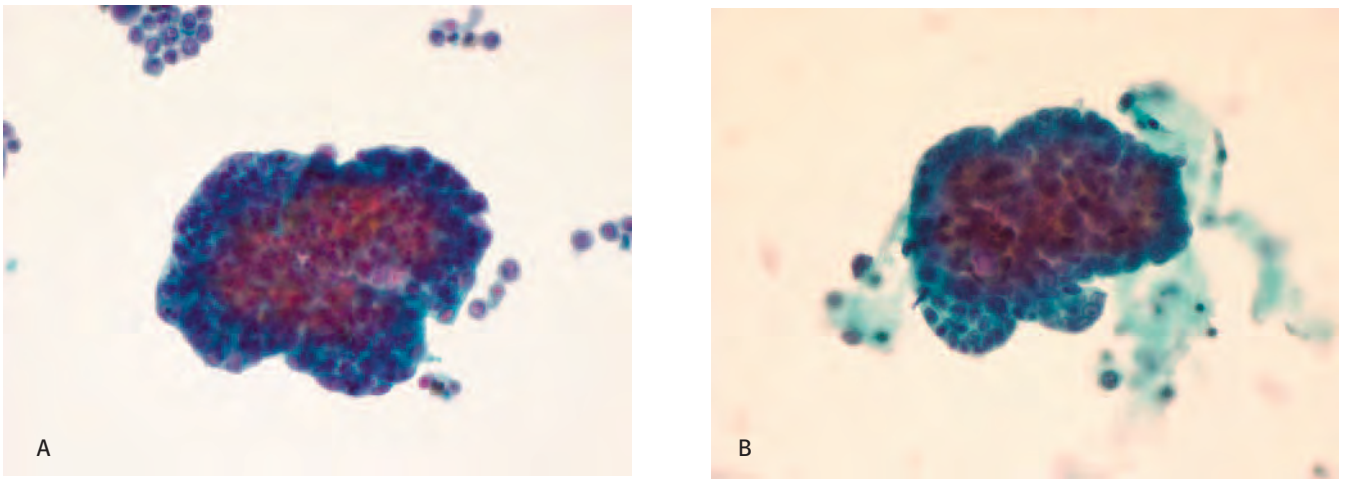

Figure 4. Papillary serous neoplasia in peritoneal washings. *A*, Serous borderline tumour with complex papillae, smooth contours, and no windows. *B*, Low-grade serous adenocarcinoma with similar architecture. Note the lack of significant nuclear atypia in both cases. (Papanicolaou stain)

In peritoneal washings, the architectural features and lack of significant nuclear atypia of the SBT and LGSC pose diagnostic challenges in that they may be under-recognized and misinterpreted as mesothelial cells or ciliated epithelium, leading to a false-negative diagnosis. No single architectural, nuclear, or cellular feature absolutely distinguishes mesothelial cells from SBT or LGSC.[15] It is the combination of cohesion, irregular group contours, intercellular windows, and absence of papillae that is specific for mesothelial cells.[15] In contrast, SBT and LGSC usually appear as smoothly contoured tightly cohesive groups or cell balls without intercellular windows (Figure 4).[8,15,18,28] They may also show complex papillae with branching, an architectural feature that is unusual for mesothelial cells, even when hyperplastic.[8] In rare cases of LGSC, but not in SBT, there may be some dyshesion.[15] A cell block may aid in recognition of these architectural findings.[29] Most SBTs and LGSCs lack the combination of marked nuclear atypia, large nuclei (>4 × the size of red blood cells [RBCs]), and large cells (≥ 8 × RBC size) that is usually identified in the HGSC.[15,18,28] This bland nuclear morphology is problematic for two reasons. Firstly, it cannot be used as a diagnostic feature to distinguish mesothelial cells from SBT or LGSC.[15,18,28] It is the combination of architectural and other nuclear features, such as mild nuclear overlap, low N/C ratio, small nuclei (2 × RBC size) and small cells (2–4 × RBC size) that distinguishes mesothelial cells from SBT and LGSC.[15] Secondly, since most SBTs and LGSCs show comparable nuclear atypia and architectural features, they are usually indistinguishable from each other in peritoneal washing samples.[15,18,22,28] This ambiguity should be reflected in the cytology report, which may read *neoplastic cells present; papillary serous neoplasm*, with a comment denoting that SBT and LGSC cannot be distinguished due to their overlapping morphological features (Table 5), and a reference to the concurrent histological sample for definitive classification. This latter comment emphasizes that if an SBT or LGSC is suspected in a peritoneal washing, then there must be correlation with the concurrent histological specimen prior to signing out the cytology report in order to avoid over-interpretation of malignancy. The finding of SBT in the peritoneum does not necessarily equate with the poorer prognosis of LGSC, unless there are invasive implants. As well, and in contrast to LGSC, a patient with SBT will not usually receive chemotherapy, unless the histology shows extra-ovarian invasive implants.

Table 5. Diagnostic Clues: Similarities between Serous Borderline Tumour and Low-Grade Serous Adenocarcinoma

Complex branching papillae
Smooth group contour, no windows
Minimal nuclear atypia and overlap
Small nuclei and cells
Cell block helpful for architecture

The recognition of HGSC is much less problematic than that of its lower-grade cousin. However, the distinction of grade 2 from grade 3 serous adenocarcinoma may be difficult, but this is not crucial for treatment purposes.[15] Dyshesion, intercellular windows, and single cells of HGSC overlap with mesothelial cell morphology, while the complex papillary architecture overlaps with SBT and LGSC morphology.[15] In most cases, however, the marked nuclear atypia (macronucleoli, irregular contours, parachromatin clearing,

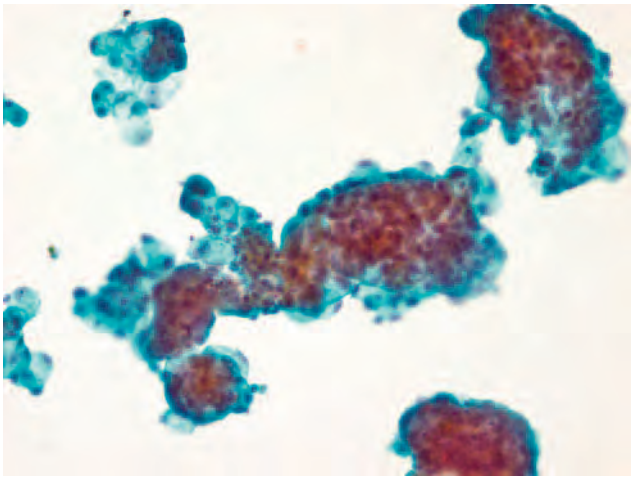

Figure 5. High-grade serous adenocarcinoma in a peritoneal washing. Large pleomorphic nuclei, large cells, and dyshesion contrast with the SBT and LGSC features shown in Figure 4. Vague papillary architecture is apparent. (Papanicolaou stain)

Table 6. Diagnostic Clues: High-Grade Serous Adenocarcinoma*

Dyshesion
May have papillae, windows, irregular contours
Marked nuclear atypia, pleomorphism
Nuclear overlap
Large nuclei and cells

*In contrast with serous borderline tumour and low-grade serous adenocarcinoma.

Table 7. Diagnostic Clues: Endometrial Adenocarcinoma

Small cells with high nuclear-to-cytoplasmic ratios
Loose dyscohesive three-dimensional clusters
Delicate cytoplasm with vacuoles
Abnormal nuclei (coarse chromatin, parachromatin clearing, nucleoli)

pleomorphism), large cells (>8 × RBC size), large nuclei (≥4 × RBC size), and nuclear overlap distinguish HGSC from mesothelial cells, SBT, and LGSC (Figure 5 and Table 6).[15]

Immunomarkers may aid in distinguishing mesothelial cells from adenocarcinoma. The use of p53 immunostaining may show some promise in identifying HGSC in peritoneal washings.[30] Although its presence is not diagnostic for neoplastic cells, cases of HGSC have shown a higher proportion of p53 immunoreactive cells compared with LGSC.[30]

The designation in a peritoneal washing of an adenocarcinoma as serous subtype is not crucial if there is a concurrent histological sample. The cytology report need only designate *adenocarcinoma* with reference to the concurrent histological sample for further classification. This approach avoids the difficult challenge of accurately subtyping high-grade adenocarcinoma arising from the gynecological tract.

Endometrial Adenocarcinoma

Peritoneal washings have been an important part of the staging procedure for endometrial carcinoma, where a positive sample previously denoted stage IIIA (FIGO 1988).[31] However, the new FIGO 2008 staging system no longer includes positive peritoneal washings for a few reasons.[32] Firstly, most patients (90–95%) with a positive peritoneal washing also have a concurrent positive extra-uterine histological sample.[5,33] Secondly, the presence of a few malignant cells in a peritoneal washing may not denote viability or implantation capability.[5] Thirdly, the studies are conflicting regarding the significance of isolated positive peritoneal cytology, which may be related to concurrent high-risk factors such as grade and depth of invasion.[5–7] Isolated positive peritoneal cytology is rare but probably significant with a small effect on survival (85% 5-year survival), but there is a lack of consensus in the literature regarding this issue.[5]

High-grade endometrial adenocarcinoma subtypes (serous, clear cell, endometrioid) are usually identifiable as high-grade adenocarcinoma in peritoneal washings and do not pose diagnostic challenges. When a concurrent histological sample is available, further subtyping of the adenocarcinoma is not crucial for treatment purposes. In contrast, the low-grade endometrioid adenocarcinoma poses some challenges in peritoneal washing interpretation, mostly related to its bland nuclear morphology and small cells, which may be overlooked and lead to a false-negative result.

Endometrioid adenocarcinoma typically appears in loose, dyscohesive three-dimensional clusters composed of small cells in peritoneal washings.[18,22] The cells have delicate cytoplasm with vacuolation, high N/C ratios, and abnormal nuclei (coarse chromatin, parachromatin clearing, prominent nucleoli) (Table 7).[18,22] The distinction from endometriosis may be problematic, as previously discussed, and lead to under-interpretation as benign. Attention to the dyshesion and nuclear atypia of malignancy may aid in the distinction. However, correlation with the concurrent histological sample may be necessary to resolve this issue.[18] In problematic cases, a differential diagnosis of endometriosis versus low-grade endometrioid adenocarcinoma may need to be rendered.

Uncommon Malignancies

Other gynecological tract malignancies are not commonly identified in peritoneal washings and may be under-recognized. Only selected uncommon malignancies are discussed here.

Peritoneal washings play a limited role in the evaluation of cervical carcinoma for a number of reasons. Firstly, cervical carcinomas are not often associated with positive peritoneal washings (2–9%), especially squamous cell carcinoma (SCC, 5%), compared with adenocarcinoma (17%).[12,34,35] Secondly, even with advanced cervical carcinoma, peritoneal washings have low sensitivity (53%), perhaps related to the preferred mode of spread for most cervical carcinomas via lymphatics.[35] Peritoneal washings may be more useful for cervical adenocarcinoma subtypes (serous, clear cell) that have a propensity for intraperitoneal spread. The main pitfall in interpretation is the distinction of non-keratinizing SCC from reactive mesothelial cells and adenocarcinoma.[17,35] Attention to the nuclear criteria of malignancy, cell dyshesion, and "hard" refractile cytoplasm may aid in identifying the malignant squamous cells. When well differentiated, the squamous features are easily visualized, especially the keratinization (orangeophilic on Papanicolaou stain, robin's-egg blue on Diff-Quik stain). Cell-in-cell engulfment and cellular vacuolation may occur in SCC, leading to a misdiagnosis of adenocarcinoma or reactive mesothelial cells.[17] A mucin stain aids in the distinction: positive in adenocarcinoma and negative in SCC.[17]

Mucinous borderline and malignant tumours of the ovary may be identified in peritoneal washings performed for staging purposes, as previously discussed. The distinction of mucinous borderline tumour from low-grade mucinous adenocarcinoma may be problematic in a peritoneal sample due to overlapping morphological features, as is the case with their serous counterparts. Again, correlation with the concurrent histological sample and the use of less specific wording in the report, such as *neoplastic cells present, mucinous neoplasm (see concurrent surgical sample)*, is prudent in these cases to avoid misinterpretation. Morphologically, mucinous borderline tumours and low-grade mucinous adenocarcinoma appear as bland columnar cells, sometimes with mucin vacuoles, arranged in cohesive clusters or monolayered sheets.[17] Extracellular mucin may be prominent as thick, homogenous material. Due to the mucolytic effects of some cytology fixatives (e.g., ThinPrep CytoLyt), there may be no or scant mucin on the slides. In contrast, high-grade mucinous adenocarcinoma shows noticeable nuclear atypia (crowding, irregular outline, irregular chromatin, large nuclei, abnormal nucleoli), three-dimensional clusters, irregular sheets, and signet-ring morphology in some.[17]

Finally, granulosa cell tumour of the ovary may be rarely identified in peritoneal washings and under-reported as negative because of overlapping morphology with mesothelial cells and difficulty in identifying the typical morphological features.[36] The most helpful clues include the scant cytoplasm and intense indentation of the nuclear membrane (grooves).[36–39] Call-Exner bodies may be identified in only some cases, and their absence does not exclude the diagnosis.[37]

Immunocytochemical Studies

Although most peritoneal washings with abnormal cells can be reported without the assistance of immunomarker studies, some cases do require ancillary testing. The fine details of immunomarker use for peritoneal washings cannot be covered in this paper, but some immunomarkers that are helpful in distinguishing mesothelial from adenocarcinoma cells are discussed. The following two general rules are suggested: (1) the selection of cases for immunomarker studies should be prudent to avoid uninformative immunomarker outcomes, and (2) a panel of immunomarkers should be used, with at least two markers for each cell type. Cases should be selected that have optimal fixation, minimal degeneration, no necrotic background, and sufficient numbers of the cells in question to be tested. More than one marker should be positive in one of the panels to identify the cell origin.

The mesothelial cell panel may include WT-1 (nuclear staining), calretinin (nuclear and cytoplasmic staining), and D2-40 (membranous staining).[10,40,41] Caution is suggested with the use of cytokeratin (CK) 5/6. Although informative in a pleural fluid, in that it distinguishes between mesothelial origin (positive) and lung adenocarcinoma (negative), CK 5/6 is positive in some non-lung adenocarcinomas.[10,41] As a result, CK 5/6 should not be used to distinguish mesothelial and adenocarcinoma cells in peritoneal washings. Thrombomodulin, HBME-1, and mesothelin are not recommended due to much lower specificity and sensitivity

compared with the other mesothelial markers.[10,40]

The best available markers to identify adenocarcinoma are B72.3, MOC-31, and Ber-EP4 because of their high sensitivity and specificity when used in combination.[10,40] Both MOC-31 and Ber-EP4 decorate adenocarcinoma cells most commonly in a membranous pattern, in contrast to B72.3, which is a cytoplasmic marker. Pitfalls with ovarian serous adenocarcinoma include (1) the expression of mesothelial markers such as WT-1, D2-40, and calretinin; and (2) a lack of expression for one, or a combination, of B72.3, MOC-31, and/or Ber-EP4 in a few cases.[40,42–44] The use of estrogen receptor and progesterone receptor may be helpful when the immunoprofile is positive for calretinin, WT-1, and Ber-EP4, in identifying serous adenocarcinoma.[40] The use of CA-125 should be avoided since both mesothelial and adenocarcinoma cells may be positive, and it is not specific as to the site of origin of the adenocarcinoma.[41]

Conclusion

Peritoneal washings for gynecological tract neoplasms are associated with important interpretative pitfalls leading to false-positive and -negative results. Correlation with concurrent histological samples is important for accurate reporting and to avoid incorrectly subtyping the tumour. Recognition of the benign mimics (ciliated epithelium, collagen balls, endometriosis, and reactive mesothelial cells) from the borderline and malignant tumours limits false-positive and -negative reporting. In some cases, an inconclusive report may have to be rendered when the cells cannot be confidently classified based on the morphology and immunoprofile. Familiarity with the morphological overlap of ovarian serous and mucinous tumours and low-grade carcinoma is essential to avoid over-reporting of these entities. A non-specific report is prudent in this latter setting (neoplastic cells, serous or mucinous neoplasm) with a comment regarding difficulty in distinguishing borderline from low-grade malignancy. Similarly, endometriosis may not always be distinguished from low-grade endometrioid adenocarcinoma, meriting an inconclusive report.

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Interest Groups as a Recruitment Strategy for Pathology

Two articles in the Spring 2012 issue of the *Canadian Journal of Pathology*, by Ford[1] and Lee et al.,[2] attempt to elucidate whether pre-clerkship curriculum design could influence recruitment in pathology. As a 1st-year medical student who places pathology among the top choices and will be co-running the school's pathology interest group next year, I believe that student-run interest groups have a huge role in recruitment for specialties.

During my 1st year of medical school, I attended various meetings hosted by student-run specialty interest groups that involved inviting physicians to talk about their work. I have observed that attending these interest group talks has a profound influence on one's perception of a specialty. For example, my private communications with my peers indicated that many students (myself included) tend to firmly "rule out" a certain specialty, for various reasons, after attending one or two of these talks about the field. It may surprise educators that students do not make such decisions primarily based on experiences gained in formal lectures. For example, some students immediately ruled out pathology just for the single reason that they could never imagine not seeing living patients. However, most failed to recognize the upside of pathology, such as a stable income, predictable hours, and minimum overhead.

Why do students fail to see the upside while heavily focusing on the downside? The reasons are multi-faceted. For example, how the speaker at these talks engages the students often affects their perception of the specialty. An engaging, energetic, jolly speaker makes the student want to come back for a future talk about this specialty, even if the specialty is initially "undesirable." Furthermore, a memorable speaker may even de-emphasize or "correct" negative pre-conceived perceptions about a specialty, which are rampant. Secondly, a resident speaker often enhances the talk in many ways. We found that some physicians who gave talks were out of date with respect to the CaRMS process and offered ambiguous answers on matching rates, resident life, and the job market. Residents were much more up to date with respect to the above aspects and even offered relevant personal anecdotes from recent years. Lastly, a lack of emphasis on interesting cases can negatively affect a talk. Everybody gets bored with a repetitive routine after a while. Does a pathologist see only slide after slide of a certain cancer for the entire 40 years of his or her career? Is what makes pathologists get out of the bed in the morning clear to the audience?

I vividly remember an outstanding talk on general surgery by a resident. Despite the fact that he openly admitted that routine work is the worst part of the specialty, he brought out so many interesting examples and anecdotes from his own residency and talked about them as if they were the "can't-miss movies of the year" that even someone with minimal aptitude for surgery would be inclined to at least observe him for a day, just to see what all the excitement is about. Certainly, the routine seemed to have no effect on the enthusiasm about his work.

In short, these talks hosted by interested groups deserve a closer study for their utility as recruitment tools for specialties. It is evident that these talks have a tremendous, if not dominant, effect on a student's perception of a specialty, at least during the pre-clerkship years. Unfortunately, these groups often suffer from a lack of funding, which hinders their ability to attract audiences.

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