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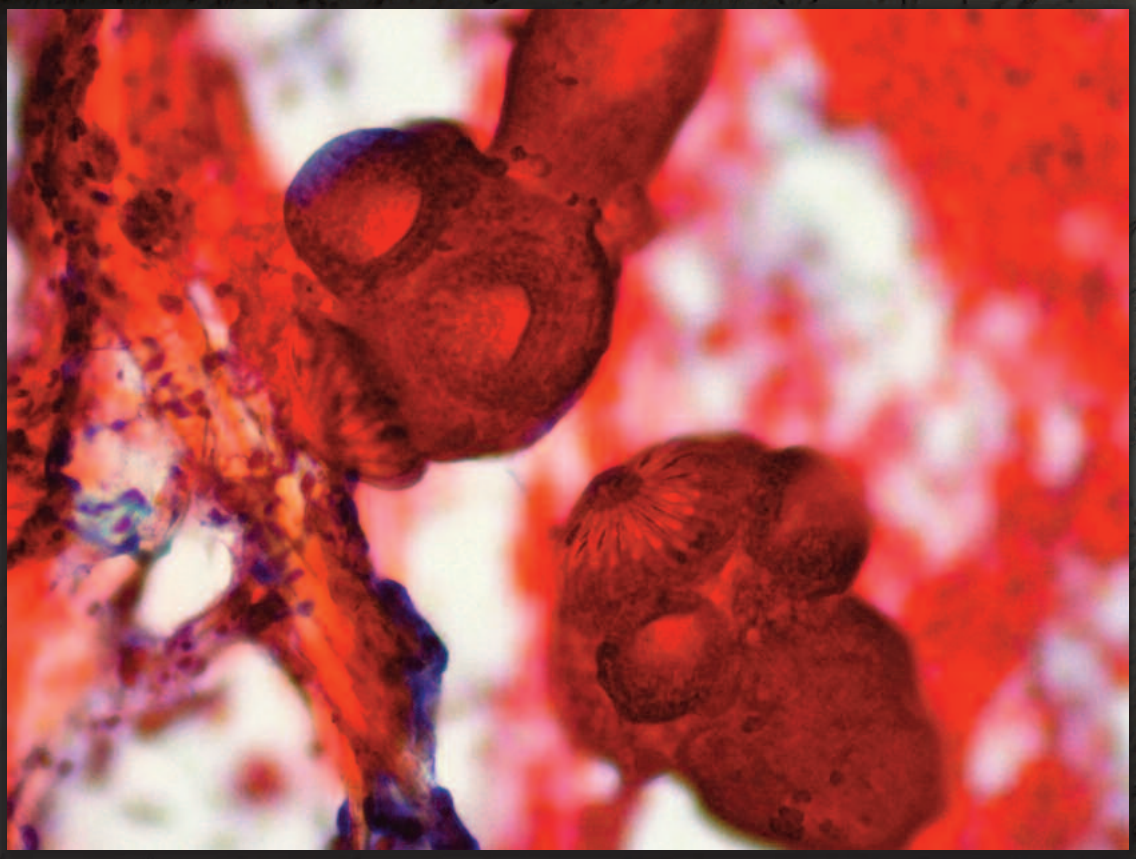

Challenging Areas in GI Biopsy Diagnosis

Hospital Autopsy Quality Assurance

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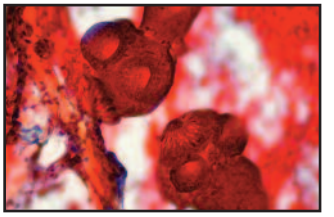

Echinococcal scolices with hooklets in a bronchoalveolar lavage specimen.

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Rapid On-Site Evaluation (ROSE): Is a Turf War Looming in Canada?

Rapid On-Site Evaluation (ROSE) is a procedure by which a cytopathologist and/or a cytotechnologist provide on-site assessment of fine needle aspiration biopsies (FNAs) performed by other physicians. These physicians have traditionally been radiologists, but now include respirologists and gastroenterologists among others. The main purpose of ROSE is to ensure that the FNA specimen is adequate for diagnosis and therefore to guide the operator to continue to do more passes if the material is deemed insufficient. Another important aim is to triage the specimen for various ancillary studies (e.g., flow cytometry, immunocytochemistry or microbiology) if necessary to ultimately reach an accurate definitive diagnosis.

Many articles have touted the advantages of ROSE, most notably an improved diagnostic yield of the FNA specimens obtained.[1-3] However, others have failed to show a benefit of ROSE, probably depending on a variety of factors, including the body site targeted and the skills of the operator performing the FNA.[4,5] Probably the biggest disadvantage of ROSE is that it is very time-consuming for the cytotechnologist and/or cytopathologist involved in the procedure. For institutions in Canada where limited budgets have resulted in reduced numbers of both cytotechnologists and pathologists, this extra task can be difficult to accommodate. The problem is compounded by the expanding trend of hospital mergers resulting in cytopathology laboratories often providing service for several physical sites that may be far apart. Where various FNA procedures may require ROSE, this adds signicant travelling time for the cytotechnologist or cytopathologist covering the ROSE service. In teaching institutions where cytopathology fellowships exist, fellows can provide welcome help; another option is telecytopathology. These options are, however, not widely available, even in most large institutions.

With the increasing popularity and the more widespread use of endobronchial ultrasound-guided FNA (EBUS-FNA) for the staging of lung cancer and of endoscopic ultrasound-guided FNA (EUS-FNA) for sampling lesions in various abdominal organs, most notably pancreas, cytopathology laboratories are under the pressure of a rapidly increasing demand for ROSE. It is always difficult to say "no" to a clinical request, but medical directors of cytopathology laboratories may have to do so or say "yes" to only a portion of the requests, depending on available resources. Directors of cytopathology laboratories should use their influence on hospital administrators to request additional resources to meet new demands such as ROSE. However, in the current economic climate of the health care system in Canada, this is a daunting task, at least in some provinces. This situation could be the spark that sets off a turf war for ROSE, spreading eventually to Canada from other countries where it has already started, such as Italy and Japan. Respirologists, radiologists, and gastroenterologists, frustrated at having been denied ROSE by their cytopathology laboratories, have decided to take matters into their own hands (or eyes!). For example, there are reports of ultrasonographers performing ROSE themselves on their EUS-guided FNA of solid masses of the pancreas, leading to a significant increase of 21% in diagnostic accuracy on final diagnoses.[6] In another report, respirologists, who had received only basic training in cytopathology, performed ROSE on transbronchial FNA, and reached an 81% overall agreement with their cytopathologist colleagues.[7] Is this turf war looming for Canada? Will cytopathologists be willing to give training to non-laboratory physicians to cover the territory that has traditionally been theirs? There is certainly a precedent in the opposite direction. Indeed, at least in the USA, many cytopathologists, sometimes after attending only a short course in ultrasound technique, are performing FNAs of superfical body sites, in particular of the thyroid, under ultrasound guidance, basically invading what has traditionally been a radiologist's terrain. Although ideally cytopathology teams should do their best to keep ROSE in their own purview, each institution will have to address the requests for ROSE in their own way, depending on human resources, the physical layout of their institution and the philosophy of their department.

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Competing interests: None declared.

L'évaluation rapide sur place : une guerre intestine en vue au Canada?

L'évaluation rapide sur place désigne l'évaluation sur place du spécimen prélevé à la cytoponction par un médecin, effectuée par un pathologiste spécialisé en cytopathologie ou un cytotechnologiste. Par le passé, le médecin effectuant la cytoponction était en général un radiologiste, mais aujourd'hui ce peut être un pneumologue ou un gastroentérologue, entre autres. L'évaluation rapide sur place a pour but principal de déterminer si le spécimen prélevé à la cytoponction est optimal en vue du diagnostic et, sinon, de guider l'exécutant dans la poursuite de la cytoponction afin de prélever suffisamment de matériel. L'évaluation rapide sur place a également pour but important le triage du spécimen en prévision de divers examens auxiliaires (cytométrie en flux, immunohistochimie ou microbiologie, par exemple) nécessaires le cas échéant pour établir un diagnostic définitif exact.

De nombreux articles font valoir les avantages de l'évaluation rapide sur place, le plus notable étant l'amélioration du rendement diagnostique des spécimens prélevés à la cytoponction[1-3]. D'autres cependant ne sont pas convaincus, en raison sans doute de divers facteurs, dont la région du corps et les aptitudes pratiques de la personne effectuant la cytoponction[4,5]. Le plus grand désavantage de l'évaluation rapide sur place est sans doute le temps que doit y mettre le cytotechnologiste ou le pathologiste spécialisé. Dans les établissements de santé du Canada où les compressions budgétaires ont entraîné la réduction du nombre de cytotechnologistes et de pathologistes, il est difficile de prévoir des ressources pour cette tâche chronophage. Le problème se complique au vu de la tendance croissante des fusions hospitalières alors que le laboratoire de cytopathologie doit offrir ses services dans plusieurs établissements qui peuvent être éloignés les uns des autres. Comme diverses biopsies par cytoponction peuvent nécessiter une évaluation rapide sur place, le cytotechnologiste ou le pathologiste spécialisé offrant le service consacrera beaucoup de temps à se déplacer, ajoutant ainsi à la durée de la tâche. Dans les établissements d'enseignement accueillant des stagiaires en cytopathologie, ces stagiaires peuvent apporter leur concours à l'exécution de cette tâche; une autre option serait de recourir à la télécytopathologie. Toutefois, ces deux options ne sont pas répandues, même dans les grands établissements de santé.

Dans le contexte de la popularité grandissante et de l'utilisation de plus en plus répandue de la cytoponction transbronchique sous guidage échographique endobronchique dans la stadification du cancer du poumon et de la cytoponction sous écho-endoscopie pour obtenir des prélèvements de lésions dans des organes abdominaux, surtout au pancréas, les laboratoires de cytopathologie croulent sous la demande d'évaluation rapide sur place en forte expansion. Il est toujours difficile de répondre par la négative à une demande de service clinique, mais il se peut que les médecins à la tête des laboratoires de cytopathologie n'aient pas d'autre choix ou alors ne pourront qu'accéder à certaines de ces demandes, en raison des ressources disponibles. Les directeurs de laboratoire devraient user de leur influence auprès des administrateurs de l'hôpital afin d'obtenir les ressources supplémentaires nécessaires pour répondre aux nouvelles demandes, notamment celles d'évaluation rapide sur place. Mais, voilà qui est loin d'être chose aisée, dans certaines provinces du moins, dans la conjoncture du système de santé au Canada. Et ce pourrait être l'étincelle qui mettra le feu aux poudres et déclenchera une guerre intestine à propos de cette intervention, une guerre qui se propagerait au Canada en provenance d'autres pays où elle fait rage déjà, comme en Italie et au Japon. Des pneumologues, des radiologistes et des gastroentérologues frustrés de se voir refuser l'évaluation rapide sur place par leur laboratoire de cytopathologie ont pris les choses en main (ou y voient eux-mêmes!). Ainsi, des échographistes effectuent l'évaluation rapide sur place des spécimens prélevés à la cytoponction sous écho-endoscopie de tumeur solide au pancréas, ce qui a amené une hausse notable de 21 % de l'exactitude du diagnostic définitif[6]. Selon un autre rapport, des pneumologues avec une formation élémentaire en cytopathologie ont obtenu un taux de concordance globale de 81 % avec leurs collègues pathologistes dans leur propre évaluation rapide sur place de spécimens prélevés à la cytoponction transbronchique[7]. Assisterons-nous à une telle guerre intestine au Canada? Les pathologistes spécialisés seront-ils disposés à former des médecins pour effectuer une tâche qui a toujours été de leur ressort? Il se pourrait que la solution soit tout autre à l'instar de ce qui se fait aux États-Unis notamment où de nombreux pathologistes spécialisés, après une formation brève en échographie, effectuent des cytoponctions échoguidées à des sites superficiels, en particulier la thyroïde, et exécutent ainsi une tâche relevant jusque-là du radiologiste. Bien que, en théorie, les équipes de

Conflits d'intérêts : aucun

cytopathologie devraient tout mettre en œuvre pour conserver l'évaluation rapide sur place, chaque établissement répondra aux demandes d'évaluation rapide à sa manière, en fonction de ses ressources humaines, de l'aménagement physique du centre hospitalier et l'orientation du service.

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References/Références

1. Andrew H. Fischer, MD; Cynthia C. Benedict, MD; Mojgan Amrikachi, MD. Five Top Stories in Cytopathology. Arch Pathol Lab Med 2013 July 2013, Vol. 137, No. 7, pp. 894-906.
2. da Cunha Santos G, Ko HM, Saieg MA, Geddie WR. "The petals and thorns" of ROSE (Rapid on-site evaluation). Cancer (Cancer Cytopathol) 2013;121: 4-8
3. Collins BT, Chen AC, Wang JF, Bernadt CT, Sanati S. Improved laboratory resource utilization and patient care with the use of rapid on-site evaluation for endobronchial ultrasound fine-needle aspiration biopsy. Cancer (Cancer Cytopathology) 2013;121:544-551
4. Cermak TS, Wang B, DeBrito P, Carroll J, Haddad N, Sidawi MK. Does on-site adequacy evaluation reduce the nondiagnostic rate in endoscopic ultrasound-guided fine-needle aspiration of pancreatic lesions? Cancer (Cancer Cytopathol) 2012;120:319-325
5. Trisolini R, Cancellieri A, Tinelli C, et al. Rapid on-site evaluation of transbronchial aspirates in the diagnosis of hilar and mediastinal adenopathy: a randomized trial. Chest 2011;139:395-401
6. Hayashi T, Ishiwatari H, Yoshida M, Ono M, Sato T, Miyanishi K, et al. Rapid on-site evaluation by endosonographer during endoscopic ultrasound-guided fine needle aspiration for pancreatic solid masses. J Gastroenter Hepatol 2013;28:656-663
7. Binfazi M, Sediari M, Ferretti M, Poidomani G, Tramacere I, Mei F, et al. The role of the pneumologist in rapid on-site cytologic evaluation of transbronchial needle aspiration. A prospective study. Chest 2014;145:60-65

Hospital Autopsy Quality Control and Assurance: The London Health Sciences Centre Experience

Rebekah Jacques, MD, Michael J Shkrum, MD, FRCPC

ABSTRACT

Purpose: Few guidelines exist for ensuring quality assurance (QA) and control for hospital autopsy. We examined QA parameters at our institution in order to make clinically useful recommendations.

Design: This study, which is a retrospective review of all hospital autopsies performed in 2009, examined QA parameters in the preanalytical, analytical, and postanalytical phases in the production of an autopsy report.

Results: The study reviewed 166 autopsies. In the pre-analytical phase, 34 (21%) autopsy authorization issues were identified, half of which required clarification of the next of kin and autopsy procedure restrictions. In the analytical phase, 67 (41%) of the reports did not have a complete microscopic blocking code, and clinico-pathologic correlations were absent in 27 (16%) autopsy reports. Photographic images were taken in 99 (60%) of the cases; however, this was mentioned in only 2 (1%) reports. The postanalytical phase identified 6 (4%) reports in which formatting, typographical, or grammatical errors were corrected. Overall, the completion times for provisional anatomical diagnoses and final reports did not conform to professional association guidelines.

Conclusions: Recommendations from this study include creating a clinician-friendly autopsy authorization form, incorporating a clinico-pathologic discrepancy classification, monitoring turnaround times, and auditing randomly selected autopsies.

RÉSUMÉ

But : Les lignes directrices en matière de contrôle et d'assurance de la qualité de l'autopsie médicale ou médicoscientifique sont rares. Nous examinons les paramètres d'assurance de la qualité à notre établissement pour formuler des recommandations utiles sur le plan clinique.

Devis : L'étude consiste en l'examen rétrospectif de toutes les autopsies effectuées à l'hôpital en 2009, portant sur les paramètres d'assurance de la qualité de la production du rapport d'autopsie dans les phases avant, pendant et après les analyses.

Résultats : Dans le cadre de l'étude, nous avons examiné 166 autopsies. Pour ce qui est de la phase précédant les analyses, nous avons relevé 34 problèmes (21 %) ayant trait à l'autorisation

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de l'autopsie, qui, pour la moitié, ont nécessité l'identification du plus proche parent et la précision des restrictions à l'intervention. Quant à la phase analytique, 67 rapports (41 %) ne comportent pas de codification complète des spécimens examinés au microscope et 27 rapports (16 %) ne font pas état des corrélations clinicopathologiques. Des photographies ont été prises dans 99 cas (60 %), mais cela n'est mentionné que dans 2 rapports (1 %). En ce qui a trait à la phase subséquente, notons 6 (4 %) rapports où des erreurs de présentation, typographiques ou grammaticales ont été corrigées. En général, le délai de production du diagnostic anatomique provisoire et du rapport final n'est pas conforme à ce que préconisent les lignes directrices de pratique d'associations professionnelles.

Conclusion : Du nombre des recommandations issues de l'étude, citons la création d'un formulaire d'autorisation d'autopsie d'utilisation conviviale pour le clinicien, l'incorporation d'une classification des divergences clinicopathologiques, la surveillance des délais d'exécution et la vérification d'autopsies choisies au hasard.

Many reports describe how the autopsy is an effective audit of clinical practice, but there are few guidelines for autopsy quality assurance (QA).[1] These guidelines primarily focus on the narrative of the report, the timeliness of its completion, and the recommendations to use autopsy results in clinical quality control programs.[2-6] Diagnostic accuracy and the procedural standards of the autopsy also need to be addressed if the autopsy is to continue to function as an effective medical audit.[7,8] The autopsy is a complex process of macroscopic, microscopic, and data interpretations that lead to post-mortem diagnoses. This process is not error-free and post-mortem diagnoses are subject to variation.[9,10]

Methods and Material

Following ethics approval, all hospital autopsies performed at London Health Sciences Centre (LHSC) from January 1 to December 31, 2009, were retrospectively reviewed. Assessment was divided into four phases: (1) the *preanalytical phase* assessed autopsy authorization issues and clinical post-mortem consultation(s); (2) the *analytical phase* reviewed various aspects of the autopsy report, which included descriptions (gross and microscopic), availability of digital images of salient gross findings, microscopic blocking code, internal pathology consultation(s), ancillary pathology, and other laboratory investigations and the clinico-pathologic correlation (CPC); (3) the *postanalytical phase* examined corrected reports and completed risk management reports, if applicable; and (4) *turnaround time* (TAT) parameters included completion of the preliminary report of provisional anatomical diagnoses (PAD) and the final report. TAT was measured in calendar days without adjusting for weekends or holidays, since services continue to be provided on these days. Factors that may influence TAT, including the number of cases per pathologist, resident involvement, pathology consultation timeliness, and slide preparation times, were examined.

Results

During the 1-year study period, 166 hospital autopsies (5.7% of in-hospital deaths) that were conducted at the LHSC were reviewed. Thirty-five of these involved pediatric and stillbirth cases. One case was excluded, in accordance with consent restrictions. Autopsies were completed by 25 pathologists and were categorized by their focus of practice (19 surgical pathologists, 3 forensic pathologists, and 3 neuropathologists).

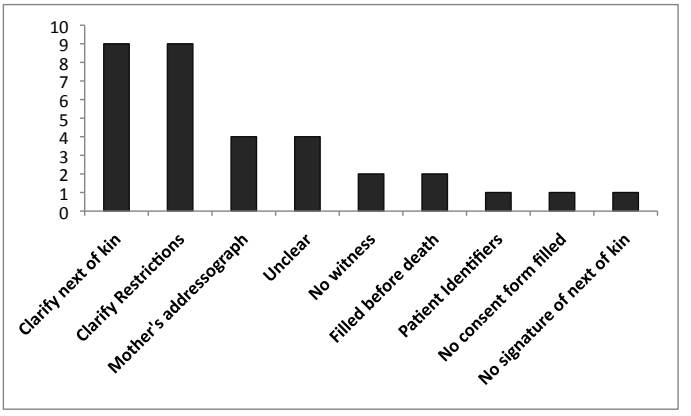


Figure 1. Summary of consent form issues.

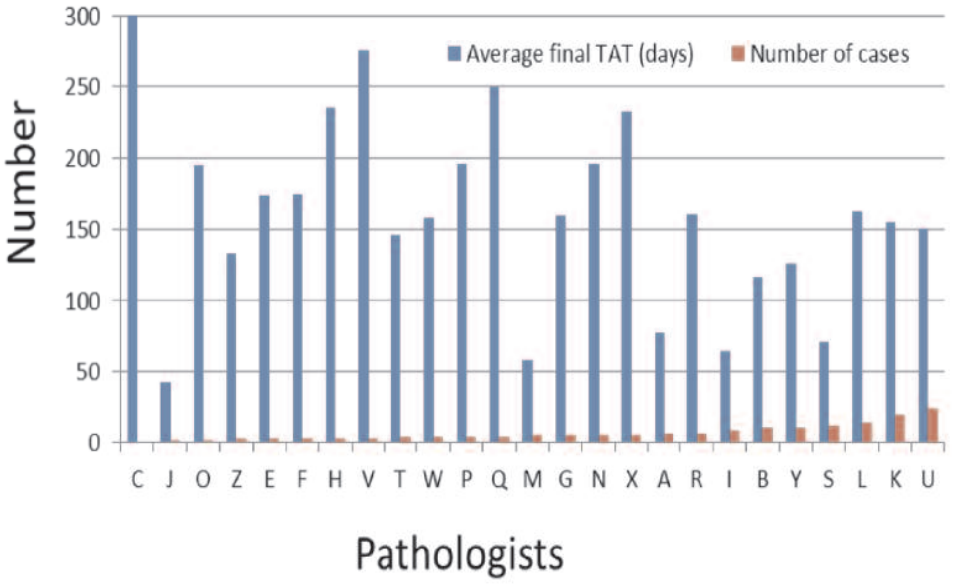


Figure 3. Lack of correlation between number of autopsies performed by individual pathologists and timeliness of reports

Table 1. Summary of turnaround times for the provisional anatomical diagnosis (PAD) and final report with respect to College of American Pathologist guidelines

	Average (Range) in days	Completed within Guidelines
PAD	5(0-37)	96 (58%)
Final Report	146(1 to 614)	57 (35%)

The preanalytical phase identified 34 autopsy authorization issues. Half of these issues required clear identification of either the next-of-kin or autopsy restrictions (Figure 1). In four cases, identification of a stillbirth or neonate required confirmation from the clinical team because the mother's name on the hospital addressograph was imprinted on the autopsy authorization form. Consent issues resulted in considerable delays (2 and 5 days) in 2 (1%) cases. Despite issues with consent, risk management reports were not completed. There were 9 (5%) clinical consultations; however, only 5 used the formal post-mortem consultation form available in the LHSC death package. This form should be completed by the physician requesting the autopsy and has sections for "Clinical Information" and "Questions to be Directed to the Pathologist." Clinicians interested in the autopsy results are also listed. Informal communications included a telephone conversation with a clinical team member, issues mentioned in a death summary report or a written note on the autopsy authorization form.

In the analytical phase, photographs were taken in 99 (60%) of cases but were mentioned in only 2 (1%) reports. This was likely a reflection of the current autopsy report template, which does not have a heading to specify that photography was performed. In 4 (2%) cases, the image's ruler label had the wrong case number designation. The report template has a heading for microscopic description. There is no specific requirement in the template for a complete microscopic blocking code which accounted for its absence in about half of the cases—67 (41%) cases. The template does have a heading for a CPC, but there were still 27 (16%) reports without one, the majority being authored by the neuropathology group. There were 116 intradepartmental pathology consultations, with the majority involving the neuropathology and cardiovascular pathology services. Reports from these services were appended to the final autopsy report. Other consultations were attributed in the microscopic description section in the final report. The ancillary investigations included immunostains, special stains,

and cytogenetic studies.

The postanalytical phase identified 6 (4%) reports in which formatting, typographical, or grammatical errors had been corrected. In the TAT phase, the average sign-out times for the provisional anatomical diagnoses and final report were 5 and 146 days, respectively (Table 1). There was no association between the timeliness and the number of autopsies performed by each pathologist (Figure 2). Resident involvement (118 [72%] of cases) increased turnaround time for the final report (159 versus116 days; $p < 0.05$, Mann-Whitney U-test). Slides were available 10 days, on average, following the autopsy.

Discussion

Preanalytical Phase

The preanalytical phase of an autopsy includes obtaining a properly completed autopsy authorization form that is signed by the appropriate next-of-kin and which indicates any autopsy restrictions. The autopsy is unusual in medical practice because consent is usually authorized by a person not receiving the procedure and is obtained by a doctor who will *not* perform the procedure.[11] There were 34 (20%) problematic hospital consents, some of which resulted in delays. The most common consent issues involved clear identification of the next-of-kin and dissection restrictions. An improperly filled autopsy authorization form is a risk management issue, but formal documentation through hospital risk management was limited. To minimize these issues the autopsy authorization form was modified by incorporating clinical input. These changes included placing the identification of the next-of-kin at the top of the form and creating a checklist format for restrictions (Figure 3).

Clinical post-mortem consultations were completed in only 8 (5%) of cases. Previous studies report frequencies of up to 72.7%.[12,13] This difference may reflect the recent introduction of these forms at our institution. When questions were actually posed by clinicians, they were always addressed by the pathologist. A similar observation was noted in previous studies.[12,14]

Analytical Phase

The analytical phase used reviewability as a means of assessing diagnostic accuracy. *Reviewability* is defined as the ability of a peer to be able to reach a conclusion, similar or different, upon assessment of sufficient information. Reviewable information available or indicated in an autopsy report includes photographic documentation of gross findings, appropriate tissue sampling for microscopy with orientation of the microscopic slides, a record of intradepartmental consultations and ancillary investigations, and a CPC. The absence of reviewable information compromises interobserver diagnostic accuracy. Reviewability allows transparency in how pathological diagnoses were achieved.

Photographs enhance a reviewer's understanding of a case, ensure transparency, and confirm completeness.[15] Photographs were frequently taken and yet were only mentioned in 2 (1%) reports. A compact disc of images was available with the hard copy of the narrative in the autopsy folder, so the need for documentation in the report may not have been deemed necessary; however, a heading in a revised autopsy report template will resolve this problem.

A microscopic block list catalogues the specific organ or tissue site of each paraffin block and slide. In 67 (41%) of cases, a complete microscopic section code was present. Incomplete section codes could reflect a pathologist's practice of consistently sampling tissues in the same order. The presence of a blocking code facilitates reviewability and is a professional guideline.[6,16]

Much of the educational function of the autopsy occurs through the CPC. A CPC is described as an objective correlation of clinical findings with autopsy gross and microscopic findings, including results of other ancillary investigations, to assist clinicians in determining the cause of death and elucidate the sequence of events leading to death. [2,16] There were 27 (16%) cases without a CPC; the majority were authored by the neuropathology group. This group performs autopsies restricted to examination of the central nervous system (CNS). The primary indication for autopsy in these cases is usually to confirm an already known clinical diagnosis and obtain tissue for research.

The overall autopsy rate was 5.7%, comparable with the average rate for teaching hospitals.[12,13,17] A low autopsy rate can diminish a pathologist's autopsy expertise, which may affect the quality of the autopsy. To ensure maintenance of autopsy competence, a dedicated autopsy team of 13 pathologists (including the 3 neuropathologists), reduced

Table 2. Proposed classification of clinico-pathological discrepancy quality assurance codes

QA Code	Description
QAA 00	No significant discrepant diagnosis identified at autopsy
QAA 01	Major diagnostic clinico-pathologic discrepancy:
QAA 02	Minor diagnostic clinico-pathologic discrepancy:
	Not applicable:
QAA 03a	Sudden death/expected death at home with no significant/recent antemortem clinical care/evaluation
QAA 03b	No anatomical/biochemical/microbiological/molecular/placental diagnosis was found following autopsy to explain either the clinical course or death or both
QAA 03c	Limited/restricted autopsy in which a pathologic diagnosis was not found to explain the clinical course or death or both

Table 3. Audit form for preanalytical, analytical, and postanalytical factors and turnaround time in hospital autopsy

Autopsy Number: _____
Date: _____
Name of Deceased: _____
Date of Postmortem: _____ Date of Review: _____
Originating Pathologist: _____ Reviewing Pathologist: _____

Preanalytical Factors	Yes	Not Applicable/No
Properly filled consent form		
Autopsy restrictions followed		
Patient identification		
Clinical postmortem consultation forms completed		

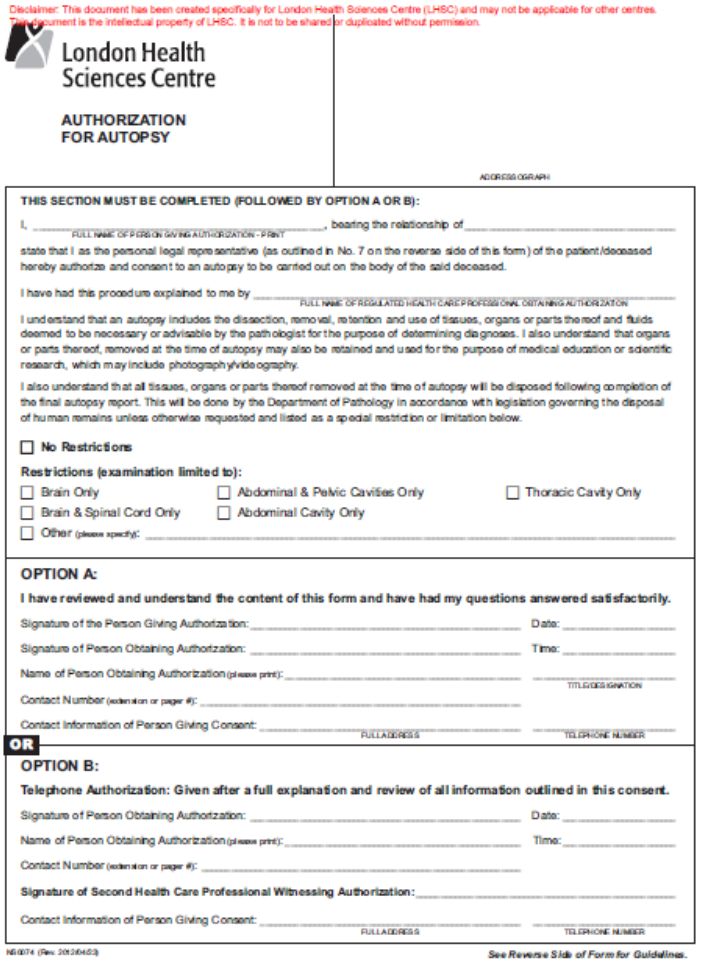
Analytical Factors	Yes	Not Applicable/No
Macroscopic interpretation consistent with description		
Photograph of gross relevant findings		
Microscopic interpretation/description supports macroscopic findings		
Complete microscopic blocking code		
Appropriate use of pathology consults		
Appropriate use of ancillary investigations		
Free of major language errors		
Clinico-pathologic correlation is reasonable		
Clinico-pathologic discrepancy code completed		

Postanalytical Factors	Yes	Not Applicable/No
Correlation between provisional and final diagnoses		
Corrected reports		

Turnaround Time	Total number of days
Post-mortem to provisional anatomical diagnosis	
Post-mortem to final anatomical diagnosis	

Disposition:
Case referred for consultation by another pathologist ❑ yes ❑ no
Feedback provided to originating pathologist ❑ yes ❑ no

Comments/suggestions:



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London Health Sciences Centre

AUTHORIZATION FOR AUTOPSY

ADDRESSOGRAPH

THIS SECTION MUST BE COMPLETED (FOLLOWED BY OPTION A OR B):

I, _____, bearing the relationship of _____
FULL NAME OF PERSON GIVING AUTHORIZATION - PRINT

state that I as the personal legal representative (as outlined in No. 7 on the reverse side of this form) of the patient/deceased hereby authorize and consent to an autopsy to be carried out on the body of the said deceased.

I have had this procedure explained to me by _____
FULL NAME OF REGULATED HEALTH CARE PROFESSIONAL OBTAINING AUTHORIZATION

I understand that an autopsy includes the dissection, removal, retention and use of tissues, organs or parts thereof and fluids deemed to be necessary or advisable by the pathologist for the purpose of determining diagnoses. I also understand that organs or parts thereof, removed at the time of autopsy may also be retained and used for the purpose of medical education or scientific research, which may include photography/videography.

I also understand that all tissues, organs or parts thereof removed at the time of autopsy will be disposed following completion of the final autopsy report. This will be done by the Department of Pathology in accordance with legislation governing the disposal of human remains unless otherwise requested and listed as a special restriction or limitation below.

☐ No Restrictions

Restrictions (examination limited to):

☐ Brain Only ☐ Abdominal & Pelvic Cavities Only ☐ Thoracic Cavity Only
☐ Brain & Spinal Cord Only ☐ Abdominal Cavity Only
☐ Other (please specify): _____

OPTION A:

I have reviewed and understand the content of this form and have had my questions answered satisfactorily.

Signature of the Person Giving Authorization: _____ Date: _____
Signature of Person Obtaining Authorization: _____ Time: _____
Name of Person Obtaining Authorization (please print): _____ _____
TITLE/DESIGNATION
Contact Number (extension or pager #): _____
Contact Information of Person Giving Consent: _____ _____
FULL ADDRESS TELEPHONE NUMBER

OR

OPTION B:

Telephone Authorization: Given after a full explanation and review of all information outlined in this consent.

Signature of Person Obtaining Authorization: _____ Date: _____
Name of Person Obtaining Authorization (please print): _____ Time: _____
Contact Number (extension or pager #): _____
Signature of Second Health Care Professional Witnessing Authorization: _____
Contact Information of Person Giving Consent: _____ _____
FULL ADDRESS TELEPHONE NUMBER

NB0874 (Rev. 2012/04/03) See Reverse Side of Form for Guidelines.

Figure 2. Improved "clinician-friendly" autopsy authorization form.

from the original 25 pathologists, was formed.

Despite the declining autopsy rate, the frequency of discrepancies between clinical and autopsy diagnoses has not changed.[12,18-21] To enhance the contribution of autopsies to the quality of clinical practice, adoption of a classification of autopsy findings based on standardized autopsy–clinical diagnosis agreement would allow for correctible and systematic errors in the diagnostic process to be integrated into educational feedback systems. Various proposals to classify diagnostic discrepancy focus on the cause and magnitude of the discrepancy.[7,12,14,21,22-25] Zarbo and colleagues suggested that the discrepancy be categorized by comparing the final autopsy and the clinical diagnoses following a pathologist's review of the clinical record.[13] We have expanded Zarbo's proposal (Table 2) by incorporating a review of the cause of death statement and assigning QA codes to each case within the final report, with the aim of providing regular follow-up to clinical departments.

Postanalytical Phase

Few corrected reports were issued, and these were for minor errors. This review did detect unexpected errors such as a signed out but unfinished autopsy report and an absent last name of the consenting next-of-kin in the autopsy report. We propose a QA review of a final report by a second pathologist to focus on all phases of the autopsy and report reviewability. A random selection of 10% of cases would be assessed by using a written evaluation form (Table 3) that focuses on reviewability prior to case sign out. These forms will be used to provide feedback to individual pathologists and recommendations for improvement of the autopsy service on an annual basis.

Turnaround Time

TAT is a measure of analytical timeliness. The PAD informs a clinical team of the gross anatomical findings, relevant clinical diagnoses or procedures, and pending investigations (e.g., a neuropathology consultation). Guidelines for communication of the PAD are variable and range from 1 to 3 days.[26-28] The completion time for PAD in our study did not conform to published guidelines. In 96 (58%) of the cases, LHSC pathologists were able to meet the 2-day guidelines. This is now being monitored weekly by secretarial staff and the Division Leader of the Autopsy Service (MJS). E-mail reminders are sent to pathologists to complete their PADs.

Guidelines for time to completion of the final report ranges from 30 to 90 days, depending on the complexity of the case.[28,29] Delay of a report is deleterious and is inefficient for the pathologist, as findings may have to be re-examined more than once with increasing time from the autopsy.[30] Only about one-third (57 cases; 35%) of the final reports were completed in 90 days, a timeline which is now the standard in the Department. Siebert acknowledged a number of causes for potential delays in autopsy reporting, including the inherent difficulty of a case, medical education of the trainees involved in the autopsy, an academic approach in writing the autopsy

report, and the need for additional ancillary tests.[31] Our study reinforced Siebert's observation that resident involvement increased TAT. Autopsies with resident involvement added an average of 6 weeks to the final TAT. Increased TAT in resident teaching institutions has been described by others as an outcome of the educational process.[32] Many of the LHSC pathologists who performed autopsies at the time of the study also have a surgical pathology focus, which demands significant time, since surgical pathology reporting has become more complex.[33] As a result, autopsy report completion can become a lesser priority.

Timeliness is monitored by providing Autopsy Team pathologists with a monthly list of all the active cases, highlighting cases that are more than 3-months-old. This is reinforced by letters to individual pathologists from the Division Leader of the autopsy service.

Formal orientation sessions, particularly for new residents, to familiarize them with autopsy protocols and reporting enhance their involvement during autopsy rotations. To improve resident TAT, a pathologist can proactively guide and monitor a resident's effort in completing a case by providing sample autopsy reports to reduce editing time and incorporate TAT as a competency in a resident's evaluation.[1,33]

At LHSC, anatomical pathology residents rotate on the autopsy service during 1-month blocks. Neuropathology residents' involvement is longitudinal and focuses on cases restricted to the examination of the central nervous system CNS. Of interest, the turnaround time for final autopsy reports was similar between neuropathology residents involved in CNS only cases and anatomical pathology residents. The Royal College initiative for competency-based medical education may provide future guidance regarding block versus longitudinal rotations to indicate which will be better in allowing residents to achieve their competency milestones.

In conclusion, current regulations require that pathology departments have a structured and active program of QA, with the goals of enhancing patient safety, minimizing error, ensuring timelines of reports, and functioning as a medical audit. We have integrated an autopsy QA program as a subset of our Department QA program as a means to improving timeliness of service and quality of reports. An annual review of data derived from the QA monitors will be completed by the Division Leader of the autopsy service. Some recommendations from this study that have already been initiated include a "clinician-friendly" autopsy consent form (see Figure 3), creation of a dedicated autopsy team, guidelines for monitoring reporting timelines, and incorporating TAT as part of the resident evaluation process. Starting an autopsy–clinical discrepancy classification, feedback to clinical teams regarding this and other service issues (e.g., issues with authorization forms) and in-depth audit of autopsy reports focusing on reviewability are the next steps.

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References

1. Young NA, Naryshkin S. An implementation plan for autopsy quality control and quality assurance. Arch Pathol Lab Med 1993;117:531–4.
2. Hutchins GM, Berman JJ, Moore WM. Hanzlick and the autopsy committee of the College American Pathologists. Practice guidelines for autopsy pathology: autopsy reporting. Arch Pathol Lab Med 1999;123:1085–92.
3. Schned AR, Mogielnicki RP, Stauffer ME. A comprehensive quality assessment program in the autopsy service. Am J Clin Pathol 1986;86:133–8.
4. Penner DW. Cost effectiveness of the autopsy in maintaining and improving the standard of patient care. Am J Clin Pathol 1978;69:250–2.
5. Friederici HHR, Sebastian M. The concordance score correlation of clinical and autopsy findings. Arch Pathol Lab Med 1984;108:515–7.
6. Hanzlick RL. The autopsy lexicon: suggested headings for the autopsy report. Arch Pathol Lab Med 2000;124:594–603.
7. Anderson RE, Hill RB, Gorstein F. A model for the autopsy-based quality assessment of medical diagnostics. Hum Pathol 1990;21:174–81.
8. Saracci R. Is necropsy a valid monitor of clinical diagnosis performance? BMJ 1991;303:898–900.
9. Uemura K, Sternby N, Vaněčk R, Vihert A, Kagan A. Grading atherosclerosis in aorta and coronary arteries obtained at autopsy. Bull W H O 1964;31:297–320.
10. Veres B, Gadaleanu V, Nennesmo I, et al. The reliability of autopsy diagnostics: inter-observer variation between pathologists, a preliminary report. Qual Assur Health Care 1993;5:333–7.
11. Williams AT, Morris D, Patel NK. Pathologists' view on consent for autopsy. Soc Med 2002;95:547–8.
12. Bayer-Garner I, Fink L, Lamps L. Pathologists in a teaching institution assess the value of the autopsy. Arch Pathol Lab Med 2002;126:442–7.
13. Chariot P, Witt K, Pautot V, et al. Declining autopsy rate in a French hospital: physicians' attitudes to the autopsy and use of autopsy material in research publications. Arch Pathol Lab Med 2000;124:739–45.
14. Zarbo R, Baker P, Howanitz P. The autopsy as a performance measurement tool-diagnostic discrepancies and unresolved clinical questions: a College of American Pathologists Q-Probes study of 2749 autopsies from 248 institutions. Arch Pathol Lab Med 1999;123:191–8.
15. Pritt B, Gibson P, Kumarasen C, et al. What is a picture worth?: digital imaging application in autopsy reports. Arch Pathol Lab Med 2004;128:1247–50.
16. Collins KA, Hutchins GM, eds. Autopsy performance and reporting. 2nd ed.

Northfield, IL: The Laboratory Accreditation Program (LAP) of the College of American Pathologists (CAP), 2003.
17. Hooper JE, Geller SA. Relevance of the autopsy as a medical tool: a large database of physician attitudes. Arch Pathol Lab Med 2007;131:268–74.
18. Kirch W, Schafii C. Misdiagnosis at a university hospital in 4 medical eras: report of 400 cases. Medicine 1996;75:29–39.
19. McPhee S. The autopsy: an antidote to misdiagnosis. Medicine 1996;76:41–3.
20. Cabot RC. Diagnostic pitfalls identified during a study of three thousand autopsies. JAMA 1912;59:2295–8.
21. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. JAMA 2003;289:2849–56.
22. Hill R, Anderson R. An autopsy-based quality assessment program for improvement of diagnostic accuracy. Qual Assur Health Care 1993;5:351–9.
23. Hall P. Do we really need a higher necropsy rate? Lancet 1999;354:2004.
24. Goldman L, Sayson R, Robbins S, et al. The value of the autopsy in three medical eras. N Engl J Med 1983;308:1000–15.
25. Battle RM, Pathak D, Humble GC, et al. Factors influencing discrepancies between premortem and post-mortem diagnoses. JAMA 1987;258:339–44.
26. Association of Directors of Anatomic and Surgical Pathology; Nakhleh R, Coffin C, Cooper K. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol 2006;37:985–8.
27. College of American Pathologists. 1992 Inspection Checklist Section VIII: Anatomic Pathology and Cytopathology. Northfield, IL: College of American Pathologists, 1992.
28. Joint Commission on Accreditation of Healthcare Organizations. 1993 Joint Commission on Accreditation Manual for Hospitals. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations, 1992.
29. College of American Pathologists, Commission on Laboratory Accreditation. 1997 Inspection Checklist Section VIII: Anatomic Pathology and Cytopathology. Northfield, IL: College of American Pathologists, 1997.
30. Siebert JR. Increasing the efficiency of autopsy reporting. Arch Pathol Lab Med 2009;133:1932–7.
31. Baker P, Zarbo R, Howanitz P. Quality Assurance of Autopsy face sheet reporting, final autopsy report turnaround time and autopsy rates. Arch Pathol Lab Med 1996;120:1003–8.
32. Hall P. Do we really need a higher necropsy rate? Lancet 1999;354:2004.
33. Sinard J, Blood D. Quality improvement on an academic autopsy service. Arch Pathol Lab Med 2001;125:237–45.

Recommendations on Quality Assurance Practices Stemming from the Findings of an Audit of Randomly Selected Negative Breast Core Biopsies

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ABSTRACT

In 2011, Diagnostic Services Manitoba (DSM), the nonprofit corporation operating public laboratories in the province of Manitoba, implemented a number of quality measures related to reporting of breast core biopsies obtained under radiological guidance. These measures included mandatory double sign-out of all breast cores with a diagnosis of atypical duct or atypical lobular hyperplasia or higher. These measures did not fully address the issue of potential false-negative reports for which double reporting was not mandated due to workload considerations. Instead, a 10% random review of negative breast core biopsies was proposed.

This audit was undertaken to both assess the accuracy of negative breast core biopsy reports and to suggest ways to reduce false-negative rates. The audit included review of 220 negative breast cores, and the diagnosis was correlated with the original. Cases with a review diagnosis of atypical duct hyperplasia (ADH) or higher were reviewed by a second pathologist.

A benign diagnosis was confirmed in 98.2% of the cases. A review diagnosis of "unsatisfactory" was made in 0.5% and missed ADH was seen in 1.4%, with two cases originally diagnosed as florid duct hyperplasia. This false-negative rate was comparable with that seen in other studies. Actions resulting from our audit included presentation of the missed ADH to pathology staff, a recommendation to stain for cytokeratin 5 or 6 (CK5/6) in questionable cases, and mandatory double reporting of cases of florid duct hyperplasia. A follow-up audit of 189 randomly selected negative core biopsies, which was performed approximately 2 years after the implementation of these changes in practice, showed a 0% false-negative rate.

The results of our audit clearly indicated that a random review of 10% of negative core biopsy reports is not an effective way to improve accuracy and mitigate patient risk. Due to the low risk of error and the workload implications, we do not recommend double sign-out of negative breast core biopsies. Targeted review is an effective approach to any quality assurance program in surgical pathology.

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RÉSUMÉ

En 2011, Services diagnostiques Manitoba, société sans but lucratif chapeautant les laboratoires publics de la province, a précisé les exigences de qualité du rapport de biopsie mammaire au trocart stéréotaxique. La confirmation obligatoire du diagnostic d'hyperplasie canalaire atypique, d'hyperplasie lobulaire atypique ou de lésions à haut risque par un second pathologiste est l'une de ces exigences. Néanmoins, la question des faux négatifs n'est pas entièrement réglée, car la confirmation d'un autre médecin n'est pas obligatoire en raison de la surcharge de travail. L'organisme propose plutôt la révision d'un échantillon aléatoire de 10 % des biopsies négatives. Nous avons entrepris la présente vérification pour évaluer l'exactitude des rapports de biopsie mammaire négatifs et suggérer des moyens de réduire le taux de faux négatif. La vérification consiste en l'examen de 200 rapports de biopsie mammaire au trocart négative et en la comparaison entre le diagnostic établi à la vérification et le diagnostic initial. En cas de diagnostic révisé d'hyperplasie canalaire atypique ou de lésions à plus haut risque, un autre pathologiste devait se prononcer.

Dans 98,2 % des cas, le diagnostic de lésions bénignes est confirmé. Dans 0,5 % des cas, le diagnostic révisé est « insatisfaisant », et l'hyperplasie canalaire atypique est passée inaperçue dans 1,4 % des cas, dont deux cas pour lesquels le diagnostic initial est celui d'hyperplasie canalaire de forme floride. Ce taux de faux négatif est comparable à celui observé par d'autres études. Par suite de notre vérification, nous avons présenté un exposé sur les cas d'hyperplasie passés inaperçus à l'effectif en pathologie et nous avons recommandé la coloration de détection de la cytokératine 5 ou 6 dans les cas douteux et la confirmation obligatoire de l'hyperplasie canalaire de forme floride par un autre pathologiste. Nous avons procédé à une vérification de suivi portant sur 189 biopsies au trocart négatives choisies au hasard deux ans après la mise en œuvre de ces modifications de la pratique; elle s'est soldée par la constatation d'un taux de faux négatif de 0 %.

Les résultats de notre vérification indiquent clairement que la révision d'un échantillon aléatoire de 10 % de biopsies négatives n'est pas une façon efficiente d'améliorer la précision diagnostique ou d'atténuer les risques pour le patient. En raison du faible risque d'erreur et des répercussions sur la charge de travail, nous ne recommandons pas la double confirmation de la biopsie mammaire négative. La révision sélective est une méthode efficiente dans le cadre du programme d'assurance de la qualité en pathologie chirurgicale.

In 2011, the Diagnostic Services of Manitoba (DSM), the non-profit corporation that runs public laboratories in the province of Manitoba, implemented a number of quality measures related to the reporting of breast core biopsies obtained under radiological guidance. Pathologists signing out these biopsies are required to report at least 200 cases a year and to enrol in continuing education related to breast pathology at least once every 2 years. All breast core biopsies with a diagnosis of atypia or higher must have the diagnosis confirmed by a second pathologist with subspecialty interest in breast pathology. Pathologists reporting breast core biopsies are also provided with online access to radiological images and reports, and a special requisition for breast cases, which required the radiologist to give a complete clinical history, including the BI-RADS score, was developed. Finally, regular radiological–pathological rounds were initiated for adjudication of cases with radiological–histological discordance.

As stringent as these measures were, they did not fully address the issue of potential false-negative biopsy reports.

Table 1. Confirmation of Negative Diagnoses

Review Report	Number of Cases[1]	Percentage of Cases
Negative diagnosis confirmed	216	98.2%
Negative diagnosis not confirmed	4	1.8%

[1]A follow-up audit of 189 negative breast core biopsies was done 24 months after changes in practice as a result of the first audit being implemented. It showed an error rate of 0%.

Table 2. Misclassified Lesions

Review Diagnosis	Number of Cases	Percentage of Cases
Unsatisfactory	1	0.5%
Atypical duct hyperplasia	3	1.4%

Double reporting of negative breast cores was not mandated due to workload considerations. Instead, a 10% random review of negative breast core biopsies was proposed. To address the efficacy of such a review, an audit was initiated to assess the histological reliability of a negative biopsy report. For the purposes of this study, a negative breast core biopsy was defined as negative for high-risk lesions, including atypical duct hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ, duct carcinoma in situ (DCIS), and invasive carcinoma.

Methods

The review included 220 sequential negative breast core biopsies from the months of June, July, and August, 2011. The biopsies were taken under stereoscopic guidance from lesions identified with mammographic screening, as well as from palpable masses. Biopsies of large palpable masses were more likely to be taken under ultrasound guidance. Indications for biopsy included calcifications, architectural distortion, and the presence of a mass. Large vacuum cores were not utilized for any of the biopsies. Pathological–radiological correlation was performed in all cases. A single senior pathologist with experience and expertise in breast pathology reviewed all of the cases. The reviewing pathologist was aware that all of the biopsies had been reported as negative but was blinded to all other histologic, clinical, and demographic information. For each biopsy, the reviewing pathologist gave a report of either "negative diagnosis confirmed" or "negative diagnosis not confirmed," with the corrected diagnosis given. Diagnosis of precursor lesions is prone to interobserver variation. Therefore, all cases which the reviewer identified as missed precursor lesions were reviewed by DSM's four subspecialty breast pathologists. The diagnosis was only changed if there was consensus among all four pathologists. Immunohistochemical staining for CK5/6 was also performed on cases of missed ADH in order to support the diagnosis.

At the conclusion of this study, we implemented several changes in practice to address the findings of the audit. This was followed 2 years later by a second audit of approximately 200 randomly selected negative core biopsy reports to determine the effectiveness of these actions.

Results

The diagnosis was confirmed as benign in 216 out of the 220 negative cases (98.2%) (Table 1). The negative breast cores showed a range of diagnoses, including normal breast tissue, stromal fibrosis, usual duct hyperplasia, sclerosing adenosis, fibroadenomatoid changes, fibroadenoma, and duct ectasia. In one case, the diagnosis after review was "unsatisfactory" (0.5%). Three cases of missed ADH (Figure 1A and Figure 2) were found on review (1.4%) (Table 2). Two of these cases had originally been diagnosed as florid duct hyperplasia. The atypical ducts in these cases showed decreased CK5/6 expression on immunohistochemical staining (Figure 1B). The third case showed ADH of columnar cell type (see Figure 2). In all cases, the radiologists who had performed the biopsies were given the relevant information.

Two of the reclassified cases, one unsatisfactory and one missed ADH, were radiologically benign. The biopsy reclassified as ADH had been performed for a fibroadenoma and the ADH was an incidental finding. No further action was taken in either case, and repeat mammography was scheduled for 1 year later for both patients. In the other two cases, biopsy had been performed because of calcifications, and the clinical information stated "rule out DCIS." In both cases, the calcifications were associated with ADH, and both patients had a subsequent lumpectomy. One lumpectomy

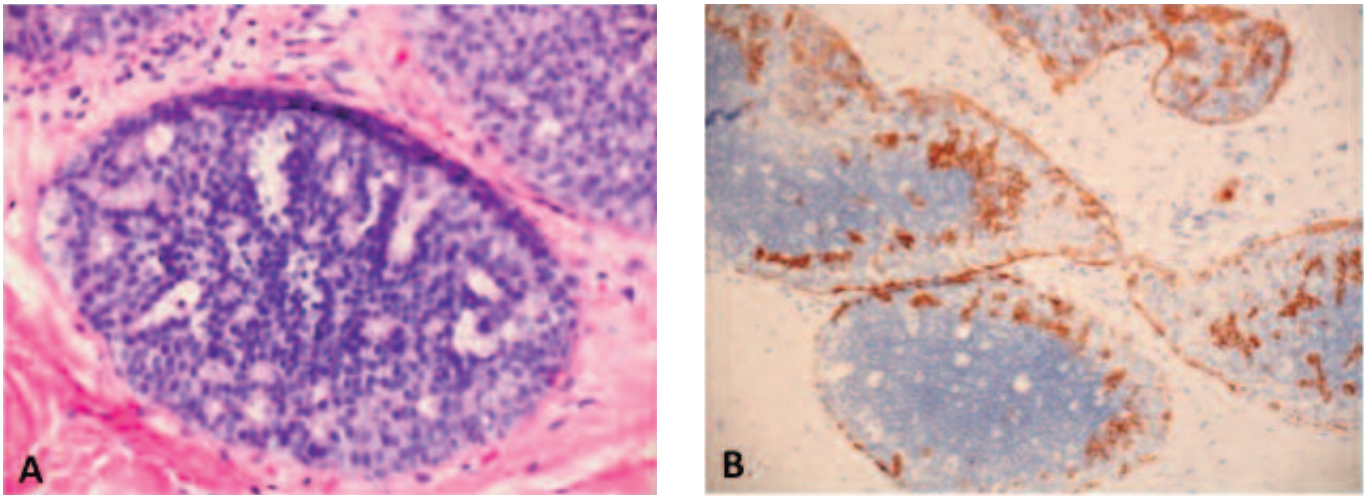

Figure 1. *A*, Atypical duct hyperplasia showing ducts filled with a monotonous population of cells. Microlumina are round, and the cells are perpendicular to the microlumina. Nuclei are smaller and more hyperchromatic at the centre than at the periphery. (Hematoxylin and eosin) *B*, Reduced imunohistochemical staining for cytokeratin 5/6 (CK5/6) in atypical duct hyperplasia. (Immunoperoxidase)

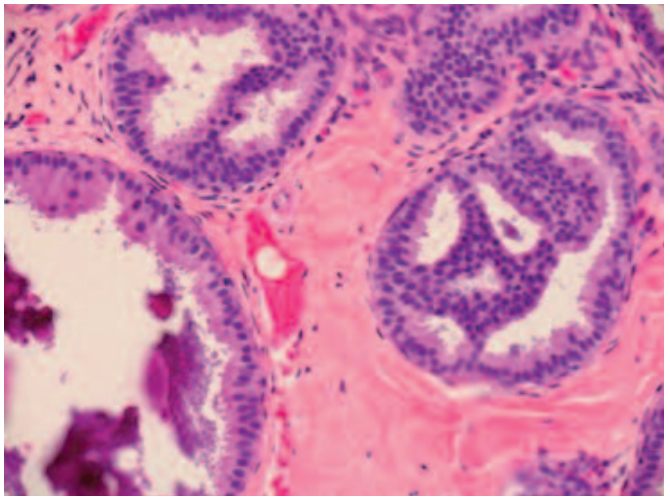

Figure 2. Ducts lined by columnar cells in atypical duct hyperplasia, columnar cell type. Some of the ducts show a proliferation of epithelial cells with a cribriform architecture. Cells are perpendicular to the microlumina; Roman arches and bridging of ducts are identified. (Hematoxylin and eosin)

showed residual ADH, but the other showed no evidence of residual disease. Neither of the lumpectomies contained DCIS or invasive carcinoma. The radiologist who had performed the biopsy on the patient with incidental ADH adjacent to a fibroadenoma decided to monitor the patient with repeat mammography in 1 year's time.

Statistical analysis was performed on the data to assess the potential value a 10% random rescreening might have to reduce the false-negative rate. False negatives of 3 out of 220 would give a proportion of 0.0136 with a 95% confidence interval (CI) of 0.0046 to 0.0393. It would, therefore, be necessary to review, on average, 73 negative tests to identify 1 false negative (95% CI 26–217). A random review of 10% of negative tests would, by definition, identify only 10% of false negatives, thus reducing the overall false-negative rate by only one-tenth. Assuming the error rate of 1.36% in this study, the random review would have reduced this only to 1.22%.

The follow-up audit that was done 24 months after implementation of the recommendations stemming from the initial audit showed a 0% false-negative rate.

Conclusion

Breast core biopsy performed under radiological guidance is an alternative to surgical excision of a breast lesion.[1-7] It is faster, is less invasive, and has fewer complications. Because the number of surgeries is reduced, there is a significant reduction in cost to the health care system. False-negative biopsies are a known risk that can delay diagnosis and treatment of a malignancy. A number of studies have evaluated false-negative diagnoses, defining a "false negative" as a core biopsy with a histological benign diagnosis followed by a high-risk or malignant diagnosis on a repeat core biopsy or subsequent surgical excision.[2,4-6,8-11] The false-negative rate is the number of false negatives

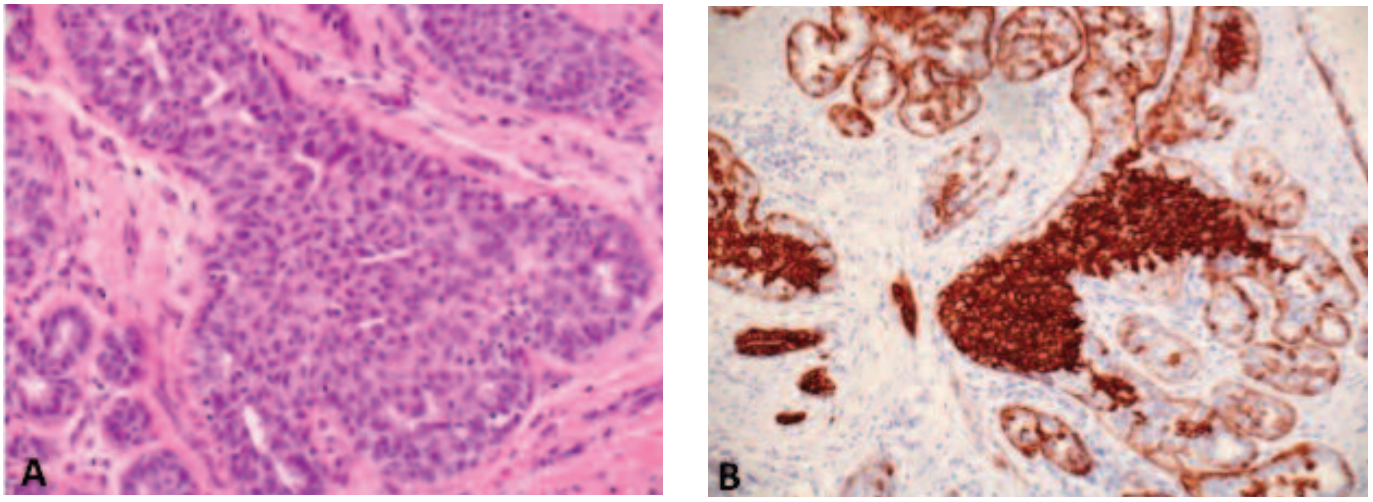

Figure 3. *A*, Usual duct hyperplasia. There is proliferation of duct epithelial cells forming solid masses predominantly in the terminal ducts. Slit-like spaces are identified with the epithelial cells lying parallel to the spaces. The epithelial cells show a streaming pattern. (Hematoxylin and eosin) *B*, Strong, diffuse imunohistochemical staining for cytokeratin 5/6 (CK5/6) in usual duct hyperplasia. (Immunoperoxidase)

divided by the number of patients diagnosed with cancer. This rate varies between 0.2 and 8%, depending on the study. Most of the studies addressing this issue have concentrated on the technical reasons, in particular sampling error, for false negatives.[5] The choices of the imaging method and the biopsy system have also been evaluated.[8,9] Sampling errors have been related to poor visualization of the lesion or needle visualization, small or deep-seated lesions, lesions in dense breasts, and heterogeneity of the lesions.[11] Biopsies with fewer than 4 or 5 cores have been shown to have a higher proportion of false-negative diagnoses.[10] The value of radiological–pathological correlation has been demonstrated.[7] Patients with false-negative core biopsies in which radiological and pathological findings do not correlate require a repeat biopsy in order to avoid a delay in diagnosis.[11] A few studies have assessed the accuracy of the pathological diagnosis in false-negative biopsies. In a study by Boba et al., the histopathology of all false-negative biopsies was reviewed.[8] Of the 988 biopsies, 22 (2.2%) were false negatives. In 14 of the 22 false-negative diagnoses, the histopathological diagnosis was changed from benign to atypical or malignant on review. False-negative diagnosis due to incorrect histopathological assessment comprised 1.5% of all histologically diagnosed cancers and atypias. The majority of the false-negative cores (12 of 14) showed atypia on review, and carcinoma was found in the other 2 cores.

Our study assessed the histopathological accuracy of negative core biopsies in our program. We defined a "false-negative diagnosis" as a diagnosis that had been changed from benign to atypical or malignant on review, and the "false-negative rate" was defined for this purpose as the number of false negatives divided by the number of negative breast cores reviewed. By this calculation, our false-negative rate was 3 or 220, or 1.4%. Like Boba et al., we found that false-negative core biopsies were most likely to be due to failure to recognize ADH.

ADH is defined as a proliferative intraductal lesion with some, but not all, of the features of DCIS.[12] The subsequent risk of invasive ductal carcinoma in a patient with ADH is 4 to 5 times that of the general population. The carcinoma could be situated elsewhere in the breast or even in the contralateral breast. Some lesions may show a combination of ADH and DCIS, or ADH, DCIS, and invasive carcinoma. A needle biopsy for a presumed carcinoma may retrieve only ADH. "Underestimated ADH" is defined as a lesion that yields ADH at needle biopsy but cancer at excision. The incidence of underestimated ADH is in the range of 20% to 60%.[7,13-16] Therefore, a diagnosis of ADH in a core biopsy requires surgical excision of the lesion, and nonrecognition of ADH in a core biopsy can lead to a delay in diagnosis and treatment.

There is, however, controversy over the need for surgery for nonobligate precursors of malignancy, including ADH. It is recommended that the decision to follow-up or proceed to surgery should depend on a combination of pathological, radiological, and clinical factors. These include, but are not limited to, degree of radiological or clinical suspicion, size of the lesion, percentage of lesion removed by the core biopsy, additional risk factors (family history, history of breast cancer), and other conditions that may increase the risk of surgery.[17] Clinical trials could clarify the impact of surgical intervention in ADH, but these trials would require accuracy in the diagnosis of ADH, since evaluation of outcome depends on a consistently correct diagnosis.

The distinction between usual duct hyperplasia and atypical duct hyperplasia can present a diagnostic problem. The criteria for a diagnosis of ADH are loosely defined and are both quantitative and qualitative. The use of only rigid qualitative criteria (features of DCIS involving 2 or fewer ductal cross-sections or less than 2 mm) is controversial, but lesion size can be used together with other criteria. ADH can be best defined as a lesion with partial involvement of ducts with structural and/or cytological changes seen in DCIS (see Figures 1A and 2). In the usual duct hyperplasia, these features are absent (Figure 3A). Immunohistochemical staining for CK5/6 can be a valuable adjunct in the differential diagnosis between usual duct hyperplasia and atypical duct hyperplasia.[18,19] Whereas the usual duct hyperplasia shows strong staining for CK5/6, ADH shows reduced expression of this marker (see Figure 1B; Figure 3B).

Because our data indicated that a random review of 10% of negative breast core biopsies would have had a very low probability of identifying the false negatives, we rejected this approach as a means of improving the diagnostic accuracy of negative breast core biopsies. This conclusion is congruent with those of other studies that also concluded that a 10% random review is costly, is time consuming, and detects few errors.[20] On the other hand, as we found in our study, a focused review of negative breast cores was effective in identifying the problem in the recognition of ADH. If we had solely relied on a 10% random review because the error rate was low, we would have been unlikely to detect this important diagnostic pitfall. The only reason to conduct a 10% random review of negative tests would be to monitor the false-negative rate of the test on an ongoing basis. Any actual identification of false negatives would be a collateral benefit of this process, rather than its intended purpose.

The quality assurance policies of some institutions mandate double sign-out for all breast core biopsies, both positive and negative. As the result of a critical incident related to a false-positive breast core biopsy, the DSM mandates double sign-out for breast core biopsies with a diagnosis of ADH or higher. Due to the low risk of error identified in our audit and the workload implications, we do not recommend double sign-out for negative breast cores.

As a result of this study, we implemented the following changes in our practice to increase the recognition of ADH and thereby reduce the false-negative rate: (1) The cases of missed ADH were presented to all DSM pathologists in a mandatory quality assurance conference; (2) pathologists were encouraged to use CK5/6 in difficult cases; and (3) pathologists were encouraged to consult on cases of florid duct hyperplasia with a second pathologist with subspecialty expertise in breast pathology. With the implementation of these changes in practice, it is noteworthy that a follow-up audit 2 years later found 0% false-negative errors. This clearly demonstrated the effectiveness of our approach to addressing the issues identified by our audit and underscores the value of targeted audits as part of any quality assurance process in surgical pathology.

References

1. Bauer RL, Sung J, Eckhert KH, Jr., et al. Comparison of histologic diagnosis between stereotactic core needle biopsy and open surgical biopsy. Ann Surg Oncol 1997;4:316–20.
2. Burns RP, Brown JP, Roe SM, et al. Stereotactic core-needle breast biopsy by surgeons: minimum 2-year follow-up of benign lesions. Ann Surg 2000;232:542–8.
3. Masroor I, Afzal S, Shafqat G, et al. Comparison of stereotactic core breast biopsy and open surgical biopsy results at a tertiary care hospital in Pakistan. Int J Women Health 2011;3:193–6.
4. Pijnappel RM, van den Donk M, Holland R, et al. PH: Diagnostic accuracy for different strategies of image-guided breast intervention in cases of nonpalpable breast lesions. Br J Cancer 2004;90:595–600.
5. Schueller G, Jaromi S, Ponhold L, et al. US-guided 14-gauge core-needle breast biopsy: results of a validation study in 1352 cases. Radiology 2008;248:406–13.
6. Verkooijen HM, Peeters PH, Buskens E, et al. Diagnostic accuracy of large-core needle biopsy for nonpalpable breast disease: a meta-analysis. Br J Cancer 2000;82:1017–21.

7. Wiratkapun C, Treesit T, Wibulpolprasert B, Lertsithichai P. Diagnostic accuracy of ultrasonography-guided core needle biopsy for breast lesions. Singapore Med J 2012;53:40–5.
8. Boba M, Koltun U, Bobek-Billewicz B, et al. False-negative results of breast core needle biopsies – retrospective analysis of 988 biopsies. Polish J Radiol Polish Med Soc Radiol 2011;76:25–9.
9. Dillon MF, Hill AD, Quinn CM, et al. The accuracy of ultrasound, stereotactic, and clinical core biopsies in the diagnosis of breast cancer, with an analysis of false-negative cases. Ann Surg 2005;242:701–7.
10. Fishman JE, Milikowski C, Ramsinghani R, et al. US-guided core-needle biopsy of the breast: how many specimens are necessary? Radiology 2003;226:779–82.
11. Youk JH, Kim EK, Kim MJ, et al. Missed breast cancers at US-guided core needle biopsy: how to reduce them. Radiographics 2007;27:79–94.
12. Rosen PP. Rosen's breast pathology. Philadephia, PA: Lippincott Williams & Wilkins, 2001:213–215.
13. Flegg KM, Flaherty JJ, Bicknell AM, et al. Surgical outcomes of borderline breast lesions detected by needle biopsy in a breast screening program. World J Surg Oncol 2010;8:78.
14. Jang M, Cho N, Moon WK, et al. Underestimation of atypical ductal hyperplasia at sonographically guided core biopsy of the breast. AJR Am J Roentgenol 2008;191:1347–51.
15. Liberman L, Holland AE, Marjan D, et al. Underestimation of atypical ductal hyperplasia at MRI-guided 9-gauge vacuum-assisted breast biopsy. AJR Am J Roentgenol 2007;188:684–90.
16. Moore MM, Hargett CW, Hanks JB, et al. Association of breast cancer with the finding of atypical ductal hyperplasia at core breast biopsy. Ann Surg 1997;225:726–31; discussion 731–33.
17. Heywang-Kobrunner SH, Nahrig J, Hacker A, Sedlacek S, Hofler H. B3 Lesions: radiological assessment and multi-disciplinary aspects. Breast Care (Basel) 2010;5:209–17.
18. Ding Y, Ruan Q. The value of p63 and CK5/6 expression in the differential diagnosis of ductal lesions of breast. J Huazhong Univ Sci Technol 2006;26:405–7.
19. Otterbach F, Bankfalvi A, Bergner S, et al. Cytokeratin 5/6 immunohistochemistry assists the differential diagnosis of atypical proliferations of the breast. Histopathology 2000;37:232–40.
20. Raab SS, Grzybicki DM, Mahood LK, et al. Effectiveness of random and focused review in detecting surgical pathology error. Am J Clin Pathol 2008;130:905–12.

ORIGINAL ARTICLE

Diagnosis of Pulmonary Echinococcosis by Bronchoalveolar Lavage Cytology

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ABSTRACT

In Canada, most cases of echinococcosis are caused by the sylvatic form of *Echinococcus granulosus*. Although several cases of pulmonary cystic echinococcosis diagnosed by fine-needle aspiration (FNA) cytology exist in the literature, such diagnoses have only rarely been made on bronchoalveolar lavage (BAL) samples; we describe such a case here.

RÉSUMÉ

Au Canada, la plupart des cas d'échinococcose sont dus à la forme sylvatique d'*Echinococcus granulosus*. Bien que la littérature fasse état de plusieurs cas de kystes hydatiques pulmonaires diagnostiqués à l'examen cytologique du spécimen prélevé par cytoponction, ce diagnostic est rarement posé par la technique de lavage bronchoalvéolaire; nous décrivons un tel cas ici.

Echinococcosis, also known as hydatid disease, is a zoonotic infection caused by the larval stage of *Echinococcus* spp. tapeworms. Human infection is most common in cattle- and sheep-raising countries, including Australia, New Zealand, Mediterranean and Middle Eastern countries, Central Europe, Russia, Northern China, and Japan. In North America, the disease is especially prevalent in Alaska and northern Canada.[1]

Most cases of human echinococcosis are caused by *E. granulosus* and *E. multilocularis*, causing (unilocular) cystic echinococcosis and (multilocular) alveolar echinococcosis, respectively. The infrequent polycystic echinococcosis, restricted to Central and South America, is caused by *E. vogeli* or *E. oligoarthrus*.[1,2] Infection with *E. granulosus* typically results in the formation of unilocular cysts that can be located in various organs, most commonly the liver (70%) or lungs (20%), with the remainder involving other organs such as kidney, spleen, brain, heart, and bone.[1-4]

The diagnosis of echinococcosis is generally based on a combination of radiographic findings and confirmatory serologic tests; in some cases, the diagnosis is made only at surgery. A few cases such as those in which no antiechinococcal antibodies are detected or in which other conditions cannot be excluded based on the imaging studies, have been diagnosed by FNA cytology.[2,5] However, because of the possibility of cyst rupture with dissemination of cyst contents and anaphylaxis, FNA is generally considered risky and contraindicated. Diagnosis of pulmonary echinococcosis by bronchoalveolar lavage (BAL) cytology has only been reported rarely;[6] here we report another such case.

Case Report

A 50-year-old First Nations woman from a small town located 300 kilometres (km) northwest of Montreal, in the province of Quebec, Canada, presented to a regional hospital with chest pain that was suggestive of coronary artery

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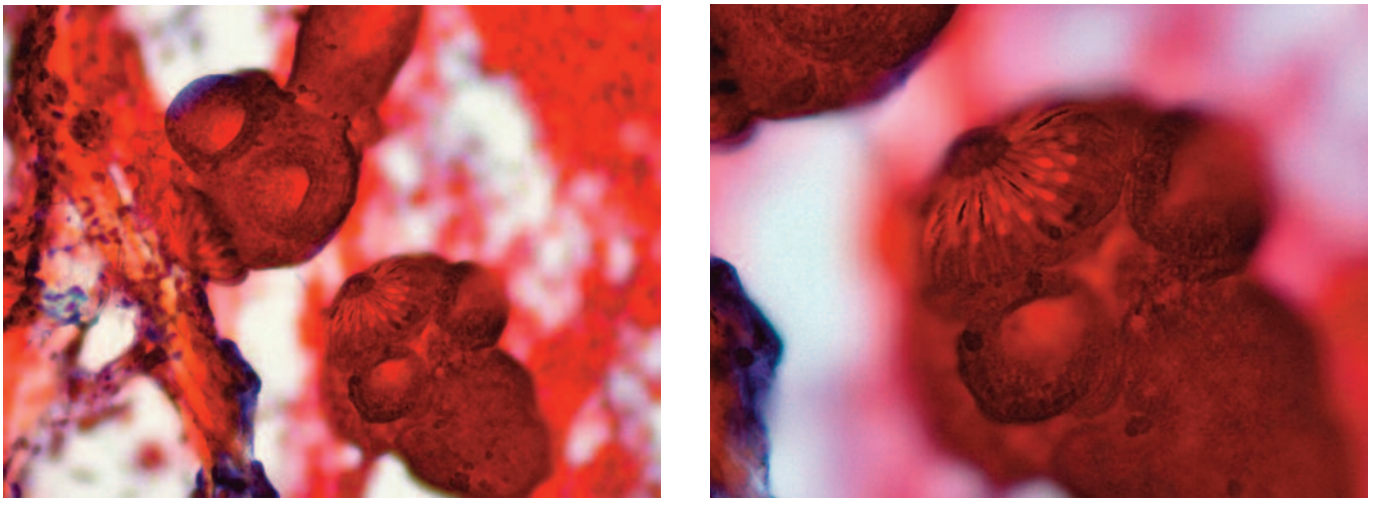

Figure 1. Numerous echinococcal scolices with hooklets are seen in the bronchoalveolar lavage (BAL) specimen. (Papanicolaou stain)

disease. Her past medical history was significant for type II diabetes mellitus and dyslipidemia. She was a former smoker, and her mother had been treated for pulmonary tuberculosis. Clinical assessment did not confirm an acute coronary syndrome, but chest radiography revealed a focus of consolidation in the left upper lobe. Moxifloxacin was given for presumed pneumonia, and the patient was discharged home.

She returned the following day with worsening fever, dyspnea, pleuritic chest pain, and a cough productive of copious amounts of white sputum. She was started on piperacillin–tazobactam and ciprofloxacin, but there was no improvement in symptoms. Computed tomography (CT) of the thorax demonstrated a 5 cm, thin-walled, fluid-filled cyst, with surrounding consolidation occupying most of the left upper lobe. Laboratory testing showed mild anemia and persistent leukocytosis of 20 to 24 $\times$ 10^9/L (normal range: 4.00–1.00 $\times$ 10^9/L) with a striking eosinophilia (absolute count of 10 $\times$ 10^9/L; normal range: 0.00–0.04 $\times$ 10^9/L). Kidney and liver function tests were normal. Serum titres of hepatitis antibodies and human immunodeficiency virus (HIV) were negative. A purified protein derivative (PPD) test was negative. Initial BAL did not yield any further diagnostic information.

Three weeks after the initial presentation, the patient was transferred to our tertiary care centre. On arrival, she was stable but still had a fever up to 39.4°C and was short of breath, with an oxygen saturation of 96% in room air. Her physical examination was unremarkable. Imaging of the abdomen was negative. CT of the thorax showed a 5.5 $\times$ 2.8 cm necrotic lesion in the anterior segment of the left upper lobe and a "tree-in-bud" pattern in the left lower lobe, suggesting aspiration of the contents of the mass. The differential diagnosis, based on radiologic findings, included atypical and/or necrotizing pneumonia, tuberculosis, pulmonary vasculitis, and aspergillosis or other fungal infection. Induced sputum was negative for acid-fast bacilli and other organisms, but cytologic examination of a second BAL fluid revealed numerous echinococcal scolices that consisted of three-dimensional structures with a stellate arrangement of hooklets at one of their extremities (Figure 1).The fluid contained a moderate amount of mixed inflammatory cells with debris and occasional degenerated macrophages. Upon questioning, the patient acknowledged contact with a dog that occasionally ventured into a wooded area.

She eventually underwent a left upper lobe lobectomy. Sections through the lung showed a well-circumscribed cyst measuring 3.5 cm in maximal dimension (Figure 2). The wall of the cyst was about 2 to 3 mm thick. The inner surface of the cyst was smooth and white. Proximally, the cyst appeared to be communicating with a bronchus, which also had a thickened white wall over a distance of 2 cm. The adjacent lung parenchyma was focally consolidated with a whitish, necrotic appearance. Histology revealed a necrotic cystic lesion containing partially degenerated ectocyst

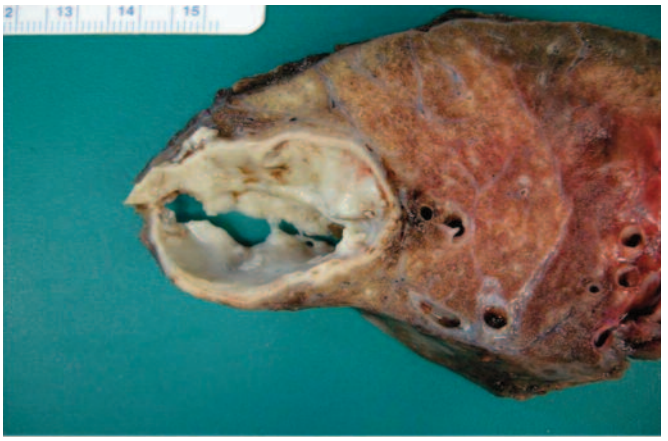

Figure 2. Macroscopic examination of the surgical specimen revealed a 5.5-cm, well-circumscribed cyst with a smooth, white inner surface and focal consolidation of the adjacent lung parenchyma.

fragments and scolices diagnostic of echinococcosis. Necrotizing pneumonia was present adjacent to the cyst.

The patient completed approximately 5 months (including 10 days before lobectomy) of therapy with albendazole. She discontinued treatment herself due to problems with alopecia and disabling dizziness, both of which appeared about 3 months into treatment. Additionally, after 4 months of treatment, the patient became severely depressed without any obvious reason or previous history of depression. All these side effects resolved spontaneously within 4 weeks of discontinuing the drug. Two years after the lobectomy, the patient remains well and free of any respiratory symptoms.

Discussion

The life cycle of *Echinococcus* organisms involves two hosts, a definitive carnivore and an intermediate herbivore. *E. granulosus*, the most frequent agent of human echinococcosis, is subdivided into pastural (or European) and sylvatic variants. In the pastural form, the predominant life cycle occurs in domestic dogs as definitive hosts, with livestock animals (e.g., sheep, horses, cattle, pigs, goats, and camels) as intermediate hosts. In the sylvatic form, the intermediate hosts are wild animals (e.g., moose, deer, or caribou), whereas the definitive host is a canine (dog, fox, or wolf) that harbors the tapeworm after ingestion of tissue from a dead infected intermediate host. Humans act as accidental hosts and typically become infected with food or water contaminated with dogs' feces containing the eggs of parasites or through direct contact with dogs.[1]

In Canada, the most common variant of echinococcosis is the sylvatic form because of infection with the "north sylvatic" or "cervid" genotype of *E. granulosus*; the case presented here fits that particular profile. The patient, who lived in a northern community, was presumably exposed to *Echinococcus* through her dog, which had likely fed on the carcass of an infected moose or deer.[1] Indeed, the most important factor identified as increasing the risk of canine echinococcosis is the access that dogs have to uncooked infected offal. It has been shown that dogs allowed to roam have a higher risk of infection because they are more likely to find and eat raw carcass meat and offal of fallen livestock.[1,7] It is estimated that between 28 and 50% of dogs in the Northwest Territories are infected with *E. granulosus*, and in recent studies in Saskatchewan, 19% to 50% of fecal samples from the dogs in northern and indigenous communities were positive for at least one helminth or protozoan parasite, compared with only 4.4% of dogs in an urban centre in Saskatchewan.[8] The risk of infection after ingestion of raw moose meat is high; it is estimated that 50% of moose in Ontario and British Columbia are infected with the parasite.[7] Hydatid cysts have also been found in wapiti, elk, reindeer, coastal deer, white tail deer, and bison. In the Northwest Territories and the northern parts of Alberta, Saskatchewan, and Manitoba, the caribou is the most common intermediate host.[1]

Echinococcosis caused by the "north sylvatic" or "cervid" genotype continues to be relatively commonly diagnosed in most Canadian provinces.[7] In contrast to the other forms, this variant is characterized by a predominantly pulmonary localization, a more benign course, and less frequent clinical complications.[7] Most patients with pulmonary echinococcosis remain asymptomatic and are diagnosed incidentally while undergoing radiologic investigations for other reasons. Symptoms develop when the cyst enlarges sufficiently to cause a mass or pressure on surrounding tissues or when the cyst ruptures into the adjacent lung, bronchus, or pleural cavity.[9] The most common symptoms described in the literature are cough (55–60%), chest pain, dyspnea, and hemoptysis.

The diagnosis of echinococcosis is only infrequently made through cytology, since percutaneous FNA of a hydatid cyst has been considered risky for fear of spillage of the cyst

contents and anaphylaxis. Degenerated hooklets can sometimes be demonstrated in the sputum, bronchial washings, and BAL or pleural fluid following cyst rupture, but only a few cases have been described in the literature.[2,10] Our case represents a rare case of pulmonary echinococcosis diagnosed in a BAL cytology specimen, presumably following rupture of the cyst into the bronchial tree. This case report raises awareness of an unusual presentation of *Echinococcus* in an appropriate clinical context as a cystic lung lesion and of the diagnostic role of exfoliative cytology.

References

1. Otero-Abad B, Torgerson PR. A systematic review of the epidemiology of echinococcosis in domestic and wild animals. PLoS Negl Trop Dis 2013;7(6):e2249.
2. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004;17:107–35.
3. Somily A, Robinson JL, Miedzinski LJ, Bhargava R, et al. Echinococcal disease in Alberta, Canada: more than a calcified opacity. BMC Infect Dis 2005;17(5):34.
4. Zhang W, Wen H, Li J, Lin R, McManus DP. Review article- Immunology and immunodiagnosis of cystic ecchinococcosis: an update. Clin Dev Immunol 2012;2012:101895.
5. Das DK, El-Sharawy M, Ayyash EH, et al. Primary hydatid cyst of the supraspinus muscle: complete removal of the germinal layer and cytodiagnosis by fine-needle aspiration. Diagn Cytopathol 2014;42:268–72.
6. Fanne RA, Khamaisi M, Mevorach D, et al. Spontaneous rupture of lung echinococcal cyst causing anaphylactic shock and respiratory distress syndrome. Thorax 2006;61:550.
7. Moro P, Schantz PM. Cystic echinococcosis in the Americas. Parasitol Int 2006;55:5181–6.
8. Jenkins EJ, Schurer JM, Gesy KM. Old problems on a new playing field: helminth zoonosis transmitted among dogs, wildlife, and people in a changing northern climate. Vet Parasitol 2011;182:154–69.
9. Santivanez S, Garcia HH. Pulmonary cystic ecchinococcosis. Curr Opin Pulm Med 2010;16:257–61.
10. Morar R, Feldman C. Pulmonary ecchinococcosis. Eur Respir J 2003;21:1069–77.

ORIGINAL ARTICLE

Retrospective Comparison of Institutional Cytological Accuracy in Warthin Tumour Diagnosis

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ABSTRACT

Purpose: We hypothesize that cytological accuracy in diagnosis of Warthin tumour (WT) at our institution has improved over time.

Study Design and Methods: A retrospective review of patients with a WT diagnosis and both fine-needle aspirate (FNA) and surgical specimens was completed for the past 8 years. All FNA specimens were prepared using a thin-layer technique. For the review, 82 patients were identified and divided into two groups based on date of FNA. True-positive (TP), false-positive (FP), and false-negative (FN) rates were calculated. Parameter of FN versus TP parameters and TP versus FP results were compared.

Results: Our institution has improved TP rates over time ($p \leq .046$). FN FNAs were more likely to have other cellular components ($p \leq 10\text{-}5$), less likely to have oncocytes ($p \leq 10\text{-}5$) and lymphocytes ($p \leq 10\text{-}5$), and had a smaller tumour size at resection ($p \leq 0.03$), compared with TP cases. FP for WT cases were more likely to occur in nonparotid locations ($p \leq .0006$). Parotid FNAs FP for WT were acinic cell carcinoma and low-grade mucoepidermoid carcinoma.

Conclusions: Cytological diagnosis of WT has improved at our institution. Associated factors include educational initiatives and changes in FNA practices by the head and neck surgeons. Mimics and key differentiating factors are reviewed.

RÉSUMÉ

But : Vérifier notre hypothèse voulant que l'exactitude du diagnostic cytologique du cystadénolymphome se soit améliorée à notre établissement.

Devis et méthodologie de l'étude : Il s'agit de l'examen rétrospectif de dossiers de patients chez qui l'on a diagnostiqué un cystadénolymphome et pour qui l'on a prélevé des spécimens à la cytoponction et à la chirurgie dans les huit dernières années. Les spécimens prélevés à la cytoponction ont été préparés selon la technique de la couche mince. Pour les besoins de l'étude, les 82 patients examinés sont répartis en deux groupes en fonction de la date de la cytoponction.

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Nous avons calculé les taux de vrai positif (VP), de faux positif (FP) et de faux négatif (FN), puis nous avons comparé les paramètres des groupes FN et VP et ceux des VP et des FP.

Résultats : Le taux de VP a augmenté à notre établissement dans cette période ($p \leq$0 0,046). Les analyses statistiques illustrent que, question de probabilité, les spécimens FN ont tendance à avoir d'autres composants cellulaires ($p \leq$ 10-5), à ne pas avoir d'oncocytes ($p \leq$ 10-5) et de lymphocytes ($p \leq$ 10-5), et la tumeur est de plus petite taille à la résection ($p \leq$ 0,03), que les spécimens VP. Dans les cas de cystadénolymphome, les FP sont principalement des spécimens provenant d'autres sites que la glande parotide ($p \leq$ 00,0006). Les spécimens issus de la glande parotide FP pour ce qui est du cystadénolymphome sont en fait un carcinome à cellules acineuses ou un carcinome mucoépidermoïde bien différencié.

Conclusion : Le diagnostic cytologique du cystadénolymphome s'est amélioré à notre établissement. Des initiatives éducatives et la modification de la technique de cytoponction des chirurgiens de la tête et du cou comptent au nombre des facteurs à l'origine de cette amélioration. Nous passons en revue des pathologies où les constats cytologiques sont semblables et les principaux traits distinctifs.

Warthin tumour (WT) is the second most common tumour of the parotid gland.[1-8] WT is an indolent neoplasm, primarily treated with surgical excision; it occasionally recurs and rarely undergoes malignant transformation.[6,8] Males are more commonly affected, with male-to-female ratios ranging from 1.1:1 to 9:1 in the literature.[2,4-5,9,10] Most patients are diagnosed between ages 50 and 80 years. [2-4,7,9-11] Multifocality and bilaterality are not uncommon.[1,6-8] Fine-needle aspiration (FNA) of salivary gland masses and cytological examination of the material is commonly used to attempt diagnosis. A typical aspirate from a WT contains oncocytes, lymphocytes, and background debris; however, inflammation, infarction, sampling error, and pathologist interpretation error are just some factors that may lead to an unclear or missed diagnosis.[7] This can lead to increased procedures, longer wait times to surgery, and increased emotional stress experienced by the patient. Occasionally, metaplastic changes can lead to a misdiagnosis of malignancy, which may result in unnecessarily extensive surgery.

On average, 11 WT diagnoses are rendered at the Queen Elizabeth II Health Sciences Centre (QEII HSC) per year. In 2003, the laboratory switched from conventional-based cytology to liquid-based preparation for all nongynecological specimens. Rapid on-site evaluation of cytology specimens for adequacy is not routine. Some pathologists perceived that the accuracy of WT diagnosis had improved over time while using liquid-based cytology; however, this had neither been confirmed nor any potential reasons identified. As well, it was felt that the diagnostic accuracy for WT may reflect accuracy of salivary gland FNA in the institution. The goal of this study was to determine if there had been improved diagnostic accuracy for WT on cytological specimens over the past 4 years compared with the previous 4 years; if so, possible reasons for improvement were to be sought.

Materials and Methods

The study was a retrospective chart review of all patients with a cytological or surgical pathology diagnosis of WT rendered at the QEII HSC over the past 8 years. The laboratory information system of the Anatomical Pathology Division was searched from November 1, 2003, to November 1, 2011, to identify all patients with a cytological diagnosis of WT or an oncocytic lesion. Next, all patients with an excision specimen diagnosed as WT from November 1, 2003, to September 28, 2012, were identified. Cytological specimens with a diagnosis of WT without a following surgical excision, as well as surgical excisions without previous cytology or cytology outside the study timeframe, were excluded.

From the reports, the following information was recorded:

surgical diagnosis, cytological diagnosis, dates of diagnoses, age and sex of the patient, site and size of tumour, and presence or absence of multifocality. Cytology reports of patients with known or suspected WT were evaluated for degree of cellularity and constituent cell types. Patients were divided into two groups based on date of FNA (November 1, 2003, to July 18, 2007; and July 19, 2007, to November 1, 2011). Cytology specimens were categorized as true positive (TP) if WT was the cytological diagnosis and the final surgical resection demonstrated WT. Cytology specimens were classified as false negative (FN) if the resection demonstrated a WT but WT was not diagnosed cytologically. This included cases where oncocytes were noted, but the possibility of a WT was not specifically mentioned, as understanding the implication of the presence of oncocytes could not be assumed on the part of the physician reading the report. Cytological specimens in which the diagnosis was indeterminate ($n = 5$), and included WT and other oncocytic neoplasms, were considered nondiagnostic and within the FN category. For the purposes of the study, unsatisfactory FNAs were deemed FN. Cytology specimens were deemed false positive (FP) for WT if the resection specimen did not demonstrate WT but the cytology had a diagnosis or favoured a diagnosis of WT.

Descriptive statistics were used to describe the patient demographics and tumour characteristics (site, size, and multifocality). Cellularity and constituent cell types (lymphocytes, oncocytes, other) were evaluated qualitatively. Standard statistical methodology was used to calculate FP, FN, and TP rates, sensitivity, and positive predictive value (PPV) in each group. Comparison of FN, FP, and TP rates between groups, FN and TP cases in terms of cellularity and cell type, and site differences between TP and FP cases were completed using the chi-square test. The Fisher Exact test was utilized in place of the chi-square test where any cell contained $n = <10$. The student t test was used to determine if tumour size was significantly different between the TP and FN cases.

This project was reviewed and approved by the Capital Health Research Ethics Board.

Results

For the review, 184 patients who had a surgical or cytological diagnosis of WT were chosen. Seventy-three patients were excluded because of lack of surgical excision specimens; 29 patients were excluded because of lack of cytology specimens. Overall, 82 patients met the study criteria, and there were 99 cytology specimens.

The study population consisted of 36 females and 46 males, with an average age of 64.1 years (range 29–92 years). There were no significant age differences between groups ($p \leq .18$) or between the male and female subgroups ($p \leq .14$ and 0.56, respectively). Most ($n = 68$) patients had one salivary gland FNA, some ($n = 11$) had two FNAs, and a few had three FNAs ($n = 3$). The study population was divided into two groups, A (FNA obtained between November 1, 2003, and July 18, 2007) and B (FNA obtained between July 19, 2007, and November 1, 2011). This represented approximately the halfway point of the study period, which began when ThinPrep tissue processing of cytological specimens was introduced at our institution. The group of seven cytopathologists reading salivary gland FNAs had been relatively stable during the entire period and included one of the authors (MJB). Group A had 49 patients (20 females and 29 males; mean age 66.1); group B had 50 patients (22 females and 28 males; mean age 61.3).

Results are summarized in Table 1. TP rates were 28.6% for Group A, and 48% for Group B ($p \leq .046$). FN rates were different between the groups: Group A had an FN rate of 65.3%, whereas it dropped to 48% in Group B. However, this difference did not reach statistical significance ($p \leq .17$). FP rates for WT were 6.1% and 4% for Group A and Group B, respectively ($p \leq .68$). Sensitivity improved in Group B (50%) versus Group A (30.4%). PPV also improved in Group B (92.3%) compared with Group A (82.4%). True negative rates and specificity could not be calculated, as capture of true negative cases was not in the scope of this project. The FN for malignancy rate was 4% for both groups. The FP for malignancy rate was 0% in both groups. The percentage of unsatisfactory FNAs was 8% for both groups.

A detailed comparison of FN and TP cytological diagnoses of WT was completed. All specimens came from the parotid gland. Tumours correctly diagnosed as WT on cytology were larger (on average 0.64 cm larger) compared with their undetected counterparts ($p \leq .03$). Oncocytes were more likely to have been detected in cases diagnosed as WT, versus

those called negative ($p \leq 10\text{-}5$). Interestingly, in a subset of six FN cases, the presence of oncocytes was recorded, but the possible diagnosis of WT was not mentioned in the report. TP cases were significantly more likely to have lymphocytes ($p \leq 10\text{-}5$) compared with FN cases. In contrast, other cells (acinar cells, squamous cells, macrophages) were more likely to be seen in FN for WT cases than in their TP counterparts ($p \leq 10\text{-}5$). Cellularity, presence of debris, and multifocality did not differ significantly.

Five FP diagnoses of WT were made (Table 2). In three of these cases, the aspirate was not from parotid tissue. However, all cytology specimens falsely diagnosed as WT were reported to have oncocytes and lymphocytes. The misdiagnoses in the parotid gland were low-grade mucoepidermoid carcinoma and acinic cell carcinoma. FP cases of WT were significantly more likely to be of nonparotid origin ($p \leq .0007$).

Discussion

The accuracy of cytological diagnosis of WT at our institution has improved since 2003. All factors examined (TP, FP, FN, sensitivity, PPV) have improved when Group A (November 1, 2003, to July 18, 2007) was compared with Group B (July 19, 2007, to November 1, 2011), although only the improvement of the TP rate was statistically significant. When attempting to discover the possible reason(s) for improvement, two specific events were brought to light, in addition to the increased familiarity of our cytopathologists with the appearance of WT in ThinPrep specimens. First, in November 2006, a didactic lecture on cytological features of WT was presented to cytotechnologists, residents, and other pathologists by one staff pathologist (MJB) interested in head and neck pathology. Second, FNA practice by the surgeons from the Division of Otolaryngology – Head & Neck Surgery (from whom the vast majority of the specimens were received) changed in 2007. Prior to this time, the FNA would be done routinely, with each specimen containing the aspirated material from one FNA. Subsequently, two separate FNAs, using two separate needles, were taken, with the combined specimens submitted in the same container. Unfortunately, exact data on when this practice began and the degree of consistency among the surgeons were not available for further analysis.

Table 1. Parameters of Accuracy of Diagnosis over Time

	Group A (November 1, 2003 – July 18, 2007)	Group B (July 19, 2007 – November 1, 2011)	p ≤
TP	28.6%	48.0%	.046
FN	65.3%	48.0%	.17
FP	6.1%	4.0%	NS
Sn	30.4%	50.0%	NA
PPV	82.4 %	92.3%	NA

TP = true positive; FN = false negative; FP = false positive; Sn = sensitivity; PPV = positive predictive value; NS =not significant; NA = not applicable

Table 2. Sites of False-Positive Diagnoses of Warthin Tumour

Cytologic Diagnosis	Final Surgical Diagnosis	Site
WT	Acinic cell carcinoma	Parotid
	Low-grade mucoepidermoid carcinoma	Parotid
	Benign salivary gland	Minor salivary gland
	Acinic cell carcinoma gland	Submandibular
	Squamous cell carcinoma	Level II lymph node

WT = Warthin tumour

This particular technique has not been evaluated in the literature, although studies of repeat FNA may provide some insight. Brennan et al. (2010), who reviewed surgical salivary tumour specimens and their previous FNAs, found that repeat FNA, where the previous FNA was adequate but nondiagnostic, provided diagnostic material in 82% of patients.[12] Similarly, simulations by Schmidt et al. (2012) showed increased adequacy with increased needle pass rates.[13] We hypothesize that improved familiarity with ThinPrep appearance, specific educational initiatives, and altered FNA practice may all have contributed to our improved cytological accuracy.

Our FP rates and PPV are within the reported range; however, our institution's sensitivity (Sn) and TP rates are below the values reported in the literature, greater than 95% and greater than 88%, respectively.[1,10-11,14] One explanation for the discrepancy is that literature rates are based on conventional cytology, whereas our study used liquid-based preparations. Studies comparing liquid-based to conventional preparations in salivary gland FNAs have

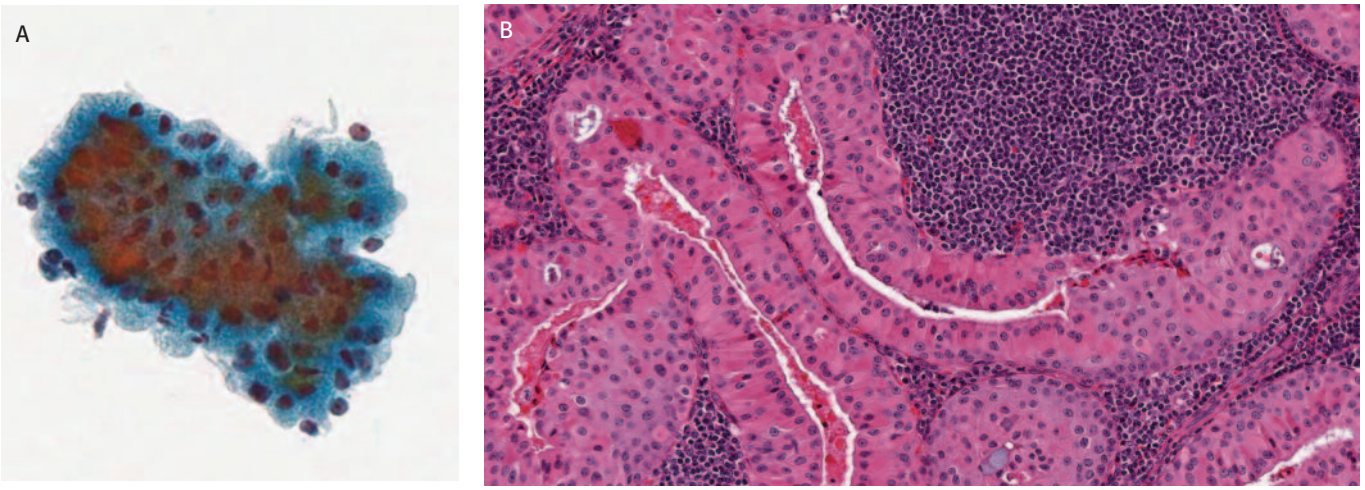

Figure 1. *A*, Oncocytes in cytology preparation. Note centrally placed nuclei, abundant cytoplasm, and fine green-blue cytoplasmic granules. *B*, Warthin tumour excision shows cysts lined by bilayered oncocytes supported by lymphocytic stroma. (*A*, Papanicolaou stain; *B*, hematoxylin and eosin)

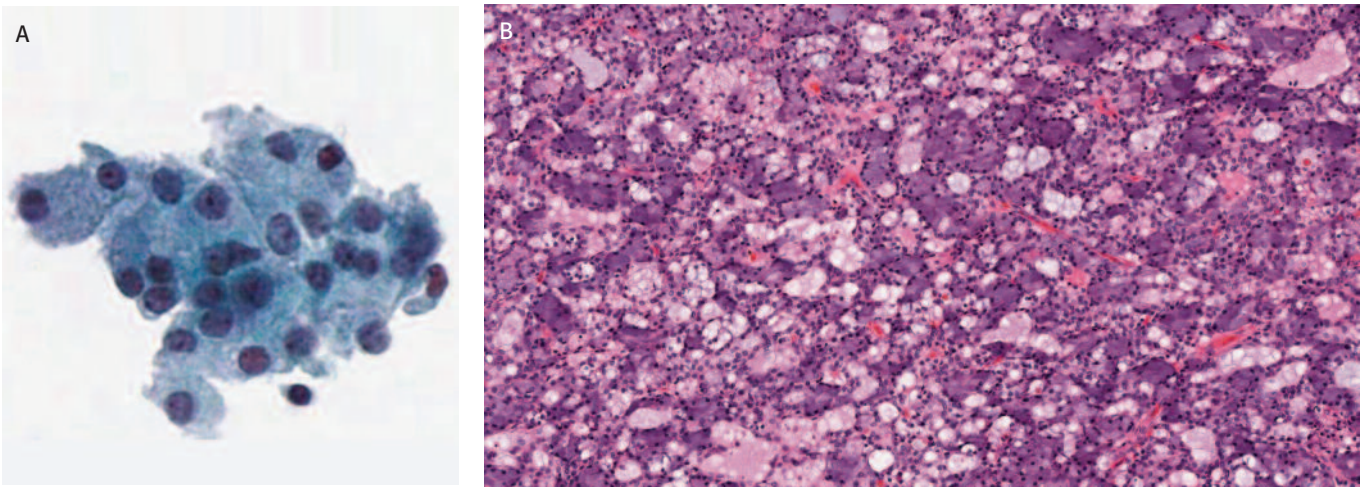

Figure 2. *A*, Acinic cell carcinoma cytology. Note slightly eccentric nucleus, variable chromocentres, and vacuolated cytoplasm with basophilic granules. *B*, Acinic cell carcinoma in surgical resection. Sheets of acinar cells are present. (*A*, Papanicolaou stain; *B*, hematoxylin and eosin)

identified that the former have decreased blood, inflammatory cells, and extracellular material.[15,16] Conventional preparations for salivary gland FNAs appear to be more accurate, with higher specificity, Sn and TP rates.[16,17] In reference to WT, studies show that liquid-based preparations have small aggregates of oncocytes, rather than sheets, and fewer lymphocytes than conventional smears.[15,17] We hypothesize that the sole use of liquid-based cytology may sometimes deprive pathologists of the diagnostic cues or materials of WT. Our Sn and TP rate have increased throughout the liquid-based preparation era, perhaps indicating adaptation to the liquid-based alterations. The differences in conventional and liquid-based cytology, especially dehiscence of oncocytes and removal of lymphocytes, may have affected our Sn, TP, and FN rates.

A contrast study of the TP and FN cases were then performed. In TP cases, the tumours were significantly larger, and the cytology specimens had significantly more oncocytes, lymphocytes, and debris, and fewer cells of other types. Although most TP cases contained more diagnostic

material than FN ones, a small subset (n = 6) of FN specimens were noted to have oncocytes in the cytology report, but WT was either not considered or not mentioned in the differential diagnosis. The cytology preparations were reviewed by two authors (AES, MJB) and could be grouped into two categories: (1) those with only rare oncocytes (n = 3) and (2) those lacking lymphocytes (n = 3). In the former, oncocytes were scant and admixed with other cells, suggesting inadequate sampling of the lesion. In the latter, oncocytes were noted and were adequate in number; however, lymphocytes were not prominent. It is important to remember that absence of lymphocytes does not exclude WT from the differential diagnosis.

The site of the specimen is another key factor to consider. All surgical WT diagnoses in this study were from the parotid gland. Indeed, one WT was originally diagnosed in a submandibular location; however, on review, portions of residual, serous salivary gland, consistent with parotid tail, were identified. There was a significant difference in tumour site in TP and FP cases. Three of the five lesions diagnosed on cytology as WT, but which represented other non-neoplastic or malignant lesions, were FNAs from nonparotid sites (submandibular gland, minor salivary gland, and a level II lymph node). The cytology of these cases was reviewed by two authors (AES, MJB). In the submandibular gland, acinic cell carcinoma cells were misinterpreted as oncocytes, which is a well-recognized diagnostic pitfall.[7,11] In the minor salivary gland resection, benign acinar cells were mistaken for oncocytes. In the level II lymph node resection, neoplastic squamous cells and enlarged lymphocytes were likely mistaken for oncocytes. It is thought that WT arise from salivary ductal inclusions in intraparotid lymph nodes.[6] A WT may arise in proximity to these other structures but likely represents origin from the parotid tail. Extreme caution should be used in suggesting a WT diagnosis in a nonparotid site. Indeed, our FN malignancy rate decreased from 4 to 2% when nonparotid sites were excluded.

The two cases falsely diagnosed as WT on cytology in the parotid received final diagnoses of low-grade mucoepidermoid carcinoma and acinic cell carcinoma on surgical resection. Upon review of the cytology specimens by two of the authors (AES, MJB), we believe that intermediate and acinar cells, respectively, were mistaken for oncocytes. Indeed, these are two of the most common cytological mimics of WT.[2,10-11]

Oncocytes are recognized on Papanicolaou cytology preparations as sheets or clusters of well-spaced, cyanophilic cells with centrally located nuclei, no atypia, and a cytoplasm with fine green-blue cytoplasmic granules.[7] To consider the diagnosis of WT or oncocytic neoplasm, a cytological preparation must include oncocytes. Lymphocytes and cellular debris may be seen in the background but are not required to raise the diagnosis. On surgical excision, there is a well-circumscribed, thinly encapsulated neoplasm composed of cystic spaces lined by bilayered, benign oncocytic epithelium with supporting lymphoid stroma.[6] Figure 1 emphasizes the cytological and histological features. Oncocytic metaplasia occurs with age and is not commonly associated with mass formation; however, nodular hyperplastic forms do exist.[1,8,18] Cytologically, there are fewer oncocytes and more normal salivary cells in the background compared with WT, although this is not always the case. Oncocytomas and WT may present similarly on cytology. Oncocytomas are rarer and have no sex predilection.[7,18] The parotid is the most common salivary gland involved.[1,7,18] The background in a cytological preparation is often clean.[7] Histologically, oncocytomas are composed of sheets or trabeculae of oncocytes separated by thin fibrovascular strands.[18] Clinical management is similar to that of WT.[8]

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy and can be a cytological mimic of WT.[7,19,20] Females are more commonly affected.[19] The parotid gland is affected in approximately 45% of cases.[8,19] The age range is broad, with the mean in the 4th decade.[20] Low-grade MEC is the most difficult to distinguish from oncocytic neoplasms. It is composed of rare squamoid cells, variable proportions of mucous cells, and abundant intermediate cells, which may mimic oncocytes.[7,11,19] Mucinous material may be present in the background.[20] Recognition of mucous cells, which can have a goblet cell or macrophage-like appearance, is critical to the diagnosis. Histologically, the tumour is composed predominantly of bland intermediate cells with cystic spaces lined by mucous cells.[19] To further confuse matters, an oncocytic variant of mucoepidermoid carcinoma exists. Careful examination for

mucous cells and cytological atypia is required.[7] Goblet cell metaplasia may be seen in WT; however, these mucous cells are often less frequent than is found in low-grade mucoepidermoid carcinoma.[7,10,19] In our case, intermediate and epidermoid cells were likely misinterpreted as oncocytes. A careful review of the cytology preparation identified mild cytological atypia, a minor mucinous background component, and extremely rare cells suspicious for mucous cells. The resection correlated with predominant intermediate cell presence, rare mucous cells, and a prominent lymphoproliferative response.

Acinic cell carcinoma is the second most common salivary gland malignancy.[7] There is a female and parotid preponderance.[7,21] Patients with acinic cell carcinoma usually present in the 3rd to 4th decade, earlier than the WT cohort.[1,8] The smear is classically cellular with a clean background.[7,11,18] The serous acinar cells, which mimic oncocytes, are often bland, with abundant, vacuolated cytoplasm and fine, basophilic cytoplasmic granules on Papanicolaou-stained preparations.[7,11] Cells often adopt a syncytial pattern and may demonstrate overlapping and crowding.[7] Apart from morphology, cell block preparation and use of special stains may aid in diagnosis if a neoplasm is suspected. Oncocytes will stain positively with phosphotungstic acid–hematoxylin because of their abundant mitochondria. Alternatively, cytoplasmic zymogen granules in acinar cells will stain positively with the Periodic acid-Schiff reagent, and are not digested by diastase.[7,21] Histologically, the tumour is composed of polygonal acinar cells with basophilic cytoplasm and round to oval, eccentrically placed nuclei, in various architectural growth patterns.[21] A review of our case revealed that acinic cells, in three-dimensional clusters of varying sizes, were mistaken for oncocytes. Figure 2 highlights the cytology and histology of acinic cell carcinoma. Careful morphologic analysis and use of ancillary studies may help to differentiate WT from acinic cell carcinoma in a cytological specimen.

In addition, a variety of salivary gland tumours may have oncocytic metaplastic change, and/or tumour associated lymphoproliferative response, which could lead to a misdiagnosis of WT when another benign or malignant tumour is present.[6,8,18,19,21]

Conclusions

Our institution has improved accuracy in cytological diagnosis of WT, likely secondary to changes in FNA practices, educational initiatives, and improved familiarity with the diagnosis in liquid-based preparations. FN cytological diagnoses may be secondary to sampling error and small tumour size and are less likely to contain diagnostic, lesional material. Oncocytes are necessary to consider WT or an oncocytic neoplasm in the differential diagnosis; lymphocytes are not required to suggest the diagnosis but should be present for a definitive diagnosis. The site of the cytological specimen is exceedingly important, and we recommend great caution when considering WT as a diagnosis in a nonparotid location. Indeed, all of our surgical WT diagnoses were from the parotid. In our cohort, and in the literature, low-grade mucoepidermoid and acinic cell carcinomas may mimic oncocytic neoplasms on cytological specimens. Careful morphological examination and use of ancillary studies may guide the pathologist to the correct diagnosis.

References

1. Torske KR. Benign neoplasms of the salivary glands. In: Thompson L, editor. Head and neck pathology: a volume in foundations in diagnostic pathology series. Philadelphia, PA: Churchill-Livingstone, 2006: 295–320.
2. Jafari A, Royer B, Lefevre M, et al. Value of the cytological diagnosis in the treatment of parotid tumors. J Otolaryngol Head Neck Surg 2009;140:381–5.
3. Jones AV, Craig GT, Speight PM, Franklin CD. The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol 2008;44:407–17.
4. Lin CC, Tsai MH, Huang CC, et al. Parotid tumors: a 10-year experience. Otolaryngol Head Neck Surg 2008;29:94-100.
5. Tian Z, Li L, Wang L, et al. Salivary gland neoplasms in oral and maxillofacial regions: A 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg 2010;39:235–42.
6. Simpson RHW, Eveson JW. Warthin tumour. In: Barnes L, Eveson J, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours: IARC WHO classification of tumours. Lyon, France: IARC Press, 2005, 263–5.
7. Krane JF, Faquin WC. Salivary gland. In: Cibas E, Ducatman B, editors. Cytology, 3rd ed. Philadelphia, PA: Elsevier, 2009, 285–318.
8. Rosai J. Major and minor salivary glands. In: Rosai J, editor. Rosai and Ackerman's surgical pathology. New York: Elsevier, 2011, 873–916.
9. Cardoso SV, do Nascimento Souza KC, de Faria PR, et al. Warthin's tumor at the Brazilian National Cancer Institute: additional evidence of homogenous sex prevalence and association with other neoplasms. J Otolaryngol Head Neck Surg 2008;70:339–43.
10. Viguer JM, Vicandi B, Jimenez-Heffernan JA, et al. Role of fine needle aspiration cytology in diagnosis and management of Warthin's tumour of the salivary glands. Cytopathology 2009;21:164–9.
11. Veder LL, Kerrebijn JDF, Smedts FM, den Bakker MA. Diagnostic accuracy of fine-needle aspiration cytology in Warthin tumors. Head Neck 2010;32:1635–40.

12. Brennan PA, Davies B, Poller D, et al. Fine needle aspiration cytology (FNAC) of salivary gland tumours: repeat aspiration provides further information in cases with an unclear initial cytological diagnosis. Br J Maxillofac Surg 2010;48:26–9.
13. Schmidt RL, Howard K, Hall BJ, Layfield LJ. The comparative effectiveness of fine-needle aspiration cytology sampling policies: a simulation study. Am J Clin Pathol 2012;138:823–30.
14. Inohara H, Akahani S, Yamamoto Y, et al. The role of fine-needle aspiration cytology and magnetic resonance imaging in the management of parotid mass lesions. Acta Otolaryngol 2008;128:1152–8.
15. Michael CW, Hunter B. Interpretation of fine-needle aspirates processed by the ThinPrep (R) technique: cytologic artifacts and diagnostic pitfalls. Diagn Cytopathol 2000;23:6–13.
16. Al-Khafaji BM, Afify AM. Salivary gland fine needle aspiration using the ThinPrep (R) Technique. Diagnostic accuracy, cytologic artifacts and pitfalls. Acta Cytol 2001;45:567–74.
17. Parfitt JR, McLachlin CM, Weir MM. Comparison of ThinPrep and conventional smears in salivary gland fine-needle aspiration biopsies. Cancer Cytopathol 2007;111:123–9.
18. Huvos AG. Oncocytoma. In: Barnes L, Eveson J, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours: IARC WHO classification of tumours. Lyon, France: IARC Press, 2005, 266.
19. Goode RK, El-Naggar AK. Mucoepidermoid carcinoma. In: Barnes L, Eveson J, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours: IARC WHO classification of tumours. Lyon, France: IARC Press, 2005,219–20.
20. Eveson JW, Thompson LDR. Malignant neoplasms of the salivary glands. In: Thompson L, editor. Head and neck pathology: a volume in foundations in diagnostic pathology series. Philadelphia, PA: Churchill-Livingstone, 2006, 321–70.
21. Ellis G, Simpson RHW. Acinic cell carcinoma. In: Barnes L, Eveson J, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours: IARC WHO classification of tumours. Lyon, France: IARC Press, 2005,216–8.

Ten Challenging Areas in Gastrointestinal Biopsy Diagnosis

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ABSTRACT

In this review article, we discuss 10 areas that provide a challenge to surgical pathologists, because of difficulties with diagnosis, terminology, or clinical associations and importance. These are all entities and issues that have been encountered in a gastrointestinal (GI) pathology consultation service. We acknowledge that the required scope and length of this article has necessarily required the omission of several other entities that may also prove difficult for surgical pathologists. Selected references only are provided to allow further review of the issues discussed.

RÉSUMÉ

Dans le présent article de fond, nous examinons 10 entités complexes en pathologie chirurgicale en raison des difficultés que posent le diagnostic, la terminologie et les manifestations ou l'importance clinique. Ce sont des entités et des problèmes auxquels un service de consultation en pathologie gastro-intestinale a été confronté. À souligner que, pour des motifs de longueur et de portée, le présent article fait abstraction de plusieurs autres entités susceptibles de poser certaines difficultés en pathologie chirurgicale. L'article se termine par une sélection de références qui permettront d'approfondir les aspects abordés ici.

Esophagitis with Eosinophils

Any number of eosinophils may be abnormal in the esophageal squamous mucosa. There are several causes, the most common of which are gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EE).[1-3] Less common causes include generalized GI eosinophilia, celiac disease, Crohn's disease, drugs, achalasia, pemphigus, and a variety of collagen vascular diseases. Clinical history is important: EE is more common in males than in females and tends to present in the 2nd decade to the 4th decade with solid-food dysphagia; patients frequently have other allergic conditions such as asthma, eczema, or food intolerances. Endoscopy also provides clues: a variety of findings such as corrugation, trachealization, white exudates or plaques, and longitudinal furrows have been described in EE. Obtaining a sufficient number of biopsies is important; eosinophilia is often patchy, and it is recommended that two to four biopsies be obtained from at least two different locations in the esophagus, usually in the distal and proximal halves of the esophagus. We encourage our endoscopists to biopsy the distal and the proximal or mid-esophagus, as finding more than a few eosinophils in the proximal or mid-esophagus or finding more eosinophils here than in the distal esophagus points away from a diagnosis of GERD. It may also be helpful

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to perform biopsies of the stomach and duodenum to exclude a generalized GI eosinophilic disorder, although this would be uncommon.

In terms of the number of eosinophils required to make the diagnosis, there is an emerging consensus that 15 or more eosinophils in at least one high-power field (HPF) is consistent with the diagnosis of EE in the appropriate clinical setting. However, in a typical case of EE, there will be many more eosinophils than this, often greater than 30 to 40 per HPF somewhere in the biopsies. There are several other findings that point toward a diagnosis of EE over GERD, including eosinophilic microabscesses (clusters of ≥4 eosinophils), superficial layering of eosinophils, numerous degranulated eosinophils, marked squamous hyperplasia, and lamina propria fibrosis (Figure 1A). These findings are much less likely to be seen in GERD than in EE. Furthermore, eosinophil counts in GERD are usually less than 10 per HPF and are highest in the distal esophagus.

Sometimes, there are borderline cases with eosinophil counts hovering around 15 per HPF, potentially without typical clinical or endoscopic features of EE or with a clinical picture more in keeping with GERD. In such cases, it may be prudent to diagnose "esophagitis with prominent eosinophils" with a comment, for example, "Although there are more eosinophils than are usually seen with GERD, the differential diagnosis includes both EE and severe GERD (or concurrent EE and GERD); additional biopsies from both the proximal and distal esophagus, after a trial of proton pump inhibitors (PPIs), may help resolve this differential."

Barrett Esophagus and Goblet Cells

Pathologists are often confounded by goblet cells. Either they are absent when the endoscopist makes a diagnosis of Barrett esophagus (BE) or they are present when unexpected. BE is defined as the presence of metaplastic columnar mucosa within the esophagus, and the American College of Gastroenterology (ACG) requires both endoscopic evidence of columnar mucosa within the esophagus and the presence of intestinal metaplasia histologically for a diagnosis of BE. A couple of awkward situations arise from the differences between these pathological and clinical definitions.[4-7]

The first is when the endoscopist submits samples from what appears to be BE, but the pathologist sees columnar mucosa without goblet cells. Notwithstanding the ACG guidelines, we agree with many other GI pathologists, especially those in Europe (and with the recent British Society of Gastroenterologists guidelines), that metaplastic columnar mucosa with an intestinal phenotype but without goblet cells represents a type of BE that has neoplastic potential. In such cases, the endoscopist's determination and communication to the pathologist of the site of the biopsies is important, but there may be clues in the biopsy to corroborate that the columnar mucosa is from the esophagus. These include intermingling of squamous islands and columnar mucosa within the same biopsy fragment, an esophageal duct underlying the columnar mucosa, and the presence of multilayered epithelium (a transitional or immature metaplastic type of epithelium) (Figures 1B and 1C). In such a situation, an appropriate diagnosis may be "columnar mucosa; non–goblet cell type" with a comment: "Goblet cells are not identified; this may represent non–goblet cell intestinalized epithelium of BE; the lack of goblet cells could be due to sampling error."

Another problematic situation arises when biopsies are submitted from the gastroesophageal junction without a clear endoscopic description of BE but intestinal metaplasia is seen histologically. BE has neoplastic potential and requires regular surveillance, but the significance of intestinal metaplasia within the gastric cardia is unclear; however, surveillance is not warranted. Intestinal metaplasia in this location, without an endoscopic Barrett segment, may be related to chronic gastritis, in which case biopsies of the distal stomach can be informative. Here, it is helpful to look for the above-listed clues to determine whether the intestinal metaplasia is esophageal, and for squamous epithelium overlying the crypts with intestinal metaplasia and hybrid glands (mucinous glands that are only partly replaced by intestinal metaplasia), all of which likely indicate true BE. In the absence of these, a diagnosis of "intestinal metaplasia present" may be rendered with the comment: "The significance of isolated intestinal metaplasia around the gastroesophageal junction is uncertain. Whether or not this represents BE will depend on whether features of BE were seen endoscopically."

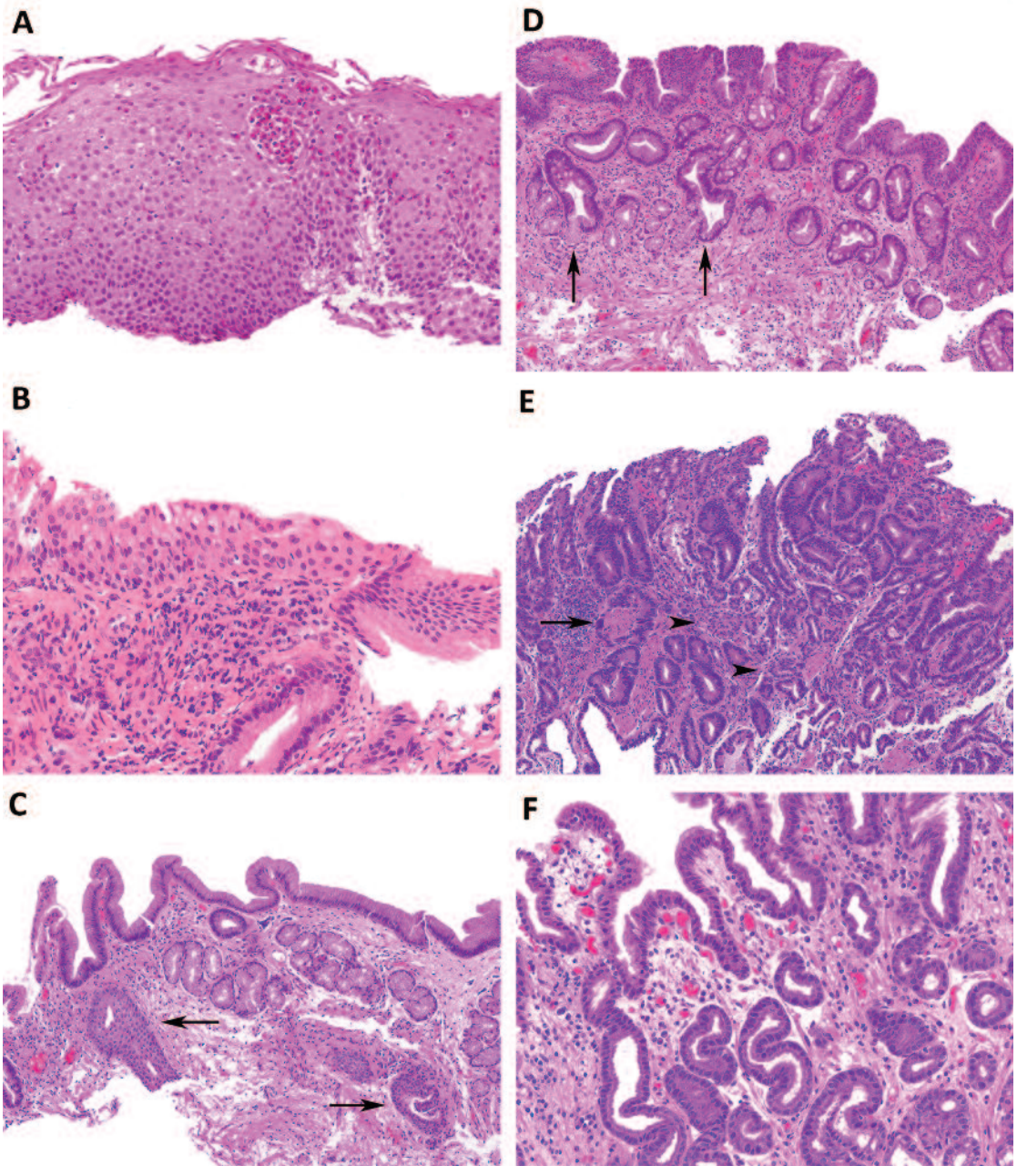


Figure 1. *A,* Eosinophilic esophagitis. There are numerous eosinophils in the squamous epithelium, with an eosinophilic microabscess. *B*, Multilayered epithelium in Barrett esophagus. This is a hybrid squamous–columnar epithelium containing mucin vacuoles. *C*, Non–goblet cell metaplastic columnar epithelium in the esophagus. The esophageal location of the biopsy can be inferred by the presence of underlying esophageal ducts (*arrows*). *D*, Barrett esophagus with low-grade dysplasia. Note the dysplastic epithelium on the surface. Hybrid glands (mixed intestinalized and mucous-type glands) are present (*arrows*). *E*, Barrett esophagus with high-grade dysplasia and features suspicious for intramucosal carcinoma. Note the gland with luminal necrotic debris (*arrow*) and the small glands that have an infiltrative growth pattern (*arrowheads*). *F*, Reactive gastropathy with tortuous pits lined by cells that have hyperchromatic nuclei and increased mitotic activity. The foveolar cells retain abundant cytoplasm, and many nuclei have small nucleoli. (Hematoxylin and eosin)

Barrett Esophagus –Dysplasia and Cancer

Dysplasia in BE is a common cause of diagnostic problems for pathologists, be it differentiating low-grade dysplasia (LGD) from reactive atypia or high-grade dysplasia (HGD) or differentiating HGD from early invasive adenocarcinoma.[8-11] Interobserver reproducibility for LGD, even among GI pathologists, is poor. LGD should be recognizable at low magnification; the features include nuclear enlargement and hyperchromasia, with or without mitoses; nucleoli are generally inconspicuous. Some degree of atypia is always present within intestinalized crypt bases but this dissipates toward the mucosal surface, and LGD is diagnosed when there is pan-crypt atypia (i.e., atypia that extends to the surface) (Figure 1D). An additional clue is that dysplastic epithelium typically shows an abrupt change to nondysplastic epithelium, whereas reactive or inflammatory atypia has a diffuse appearance and fades in and out within a biopsy. We have also noted that tufted epithelium is more often reactive (personal observations).

The term "indefinite for dysplasia" should be used when there is atypia beyond what may be readily recognized as reactive epithelium but falling short of what is obviously dysplastic. This situation usually arises when there is abundant neutrophilic inflammation. Traditionally, the term "indefinite for dysplasia" has also been used when dysplasia-like atypia is present in crypt bases but absent on the surface, because of either maturation or artifactual absence of surface epithelium. Recently, however, the entity "crypt dysplasia" has been reported; proponents suggest the use of this term when atypia within crypt bases is greater than expected with intestinal metaplasia alone but surface maturation is present. Some authors advocate including "crypt dysplasia" within the traditional category of LGD. Although the evidence for crypt dysplasia is convincing, we have difficulty and reservations about reporting this as LGD, since it seems likely that the interobserver reproducibility of LGD, which is already poor, will be worse. We prefer to report such cases as "indefinite for dysplasia" with a comment such as: "Although this case is interpreted as indefinite for dysplasia, there are features that may represent so-called 'crypt dysplasia.' Repeat short interval biopsies are suggested to further assess the presence and degree of dysplasia."

HGD is more easily recognized, with better interobserver reproducibility, being characterized by epithelium with severe nuclear atypia, often with prominent nucleoli, loss of nuclear polarity, and (often) architectural complexity. Nevertheless, discomfort arises because of the importance of this diagnosis, since, given the risk of malignancy of up to 50% in these patients, it leads in most cases to definitive therapy. Thus, the recommendation is that a second opinion from an "expert" pathologist should be sought to confirm HGD. There is a similar risk of malignancy with any grade of dysplasia that is endoscopically polypoid, and such cases should also have mandatory second review. What constitutes an "expert" in these circumstances is open to debate; we contend that review by a competent pathologist experienced in assessing GI biopsies would be appropriate.

Another challenging diagnosis is early invasive adenocarcinoma, especially distinguishing it from HGD. Features that distinguish intramucosal adenocarcinoma from HGD include effacement of the lamina propria by confluent glands (cribriforming without intervening stroma) and invasion of single cells or small cell clusters; the presence of neoplastic glands with intraluminal necrotic debris also most often indicates intramucosal invasion (Figure 1E). If only the latter feature is seen, we report "at least high-grade dysplasia; suspicious for intramucosal adenocarcinoma." In cases of unequivocal invasion, we report "adenocarcinoma, at least intramucosal invasion present," given that even lamina propria invasion in the esophagus signifies a T1 cancer with the potential for lymph node metastases. It is unwise to diagnose submucosal invasion in mucosal biopsies from the esophagus, even if there is apparent traverse of muscularis mucosae, since duplication of the muscularis mucosae is often present with BE. A diagnosis of submucosal invasion may preclude endoscopic mucosal resection, given the high risk of lymph node metastases associated with submucosal invasion.

Pseudodysplastic Changes in Reactive Gastropathy

Reactive gastropathy, also known as chemical gastropathy, is a form of injury to the gastric mucosa induced by chemicals; the chemicals are most commonly drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or steroids but also include alcohol and bile, when there is bile

reflux. This gives rise to a characteristic constellation of histological changes that include foveolar hyperplasia, mucin depletion, lamina propria edema, congestion, and proliferation of smooth muscle bundles in the lamina propria. In cases that have an acute component, with or without erosive changes, the foveolar epithelium can look markedly atypical and may be confused with dysplasia (either conventional adenomatous or foveolar types) (Figure 1F). In reactive gastropathy, both cytoplasmic basophilia and nuclear hyperchromasia within mucin-depleted foveolar epithelium may stand out against the pale, edematous lamina propria to give an initially alarming appearance. However, in our experience, the atypia associated with reactive gastropathy has a characteristic morphology and looks different from dysplasia.

First, the characteristic elongation and tortuosity of pits, as well as the lamina propria edema and smooth muscle proliferation of reactive gastropathy, are typically lacking with dysplasia. Second, the cytology of the foveolar epithelium in reactive gastropathy is different from dysplasia. The foveolar epithelial cells in reactive gastropathy are cuboidal and have hyperchromatic nuclei, typically devoid of much nuclear detail, taking on a smudged appearance. Nuclear size and shape vary from cell to cell more than in dysplasia; however, on average, the nuclear size is smaller than with dysplasia, and significant nuclear crowding or pseudostratification is lacking. Also, in reactive gastropathy, there is an increase in nuclear-to-cytoplasmic ratio, which is mainly due to decreased cytoplasm or mucin depletion. With dysplasia, the increase in nuclear to cytoplasmic ratio is mainly due to increased nuclear size. Finally, the atypia of reactive gastropathy is typically diffuse, possibly fading in and out within biopsies. By contrast, a sharp demarcation between atypical and non-atypical epithelium is feature of dysplasia. Once these features are recognized, the atypia of reactive gastropathy can usually be readily distinguished from true dysplasia.

Duodenal Intraepithelial Lymphocytosis

The number of duodenal biopsies with normal or near-normal villous architecture and increased numbers of intraepithelial lymphocytes (IELs) appears to be increasing. Such cases can be a conundrum for pathologists (and treating physicians) because the causes are protean, and the way in which they should be reported is not always clear. [12,13] Normal duodenal mucosa has a villus-to-crypt ratio of around 3:1, but pathologists should be aware that in the proximal duodenum (especially the duodenal bulb), villi are often shorter and appear somewhat distorted. IELs are normally present, but there should be less than 20 to 25 lymphocytes per 100 enterocytes. However, we count IELs rarely and typically rely on a gestalt approach for assessing their number. In rare borderline cases, a simple procedure to determine if there are increased IELs is to count lymphocytes per 20 enterocytes at the tip of a few villi; greater than 5 lymphocytes per 20 enterocytes indicates intraepithelial lymphocytosis.

Biopsies with normal villous architecture and increased IELs arise in several circumstances. The three most common causes are early celiac disease, gastric *Helicobacter pylori* infection, and medications, especially NSAIDs, but it is also reported with PPI use. Other causes include viral infection, food allergy, giardiasis, small intestine bacterial overgrowth, tropical sprue, Crohn's disease, and various immunological or autoimmune disorders. Gastroenterologists are typically most interested in whether any changes present reflect celiac disease. Several studies have investigated whether the location of the IELs (villous tip versus mid-villus or base) or the level of IEL increase can distinguish celiac disease from other causes. The results of these studies are variable, and we do not find this reliable. Correlation with serology, namely, tissue transglutaminase (TTG), is the most helpful approach, and intraepithelial lymphocytosis associated with an elevated TTG is highly likely to represent celiac disease.

In terms of reporting, we diagnose these cases as "intraepithelial lymphocytosis with normal villous architecture" and we add a comment to address the most common associations: "Intraepithelial lymphocytosis with normal villous architecture is a nonspecific finding that may be associated with several causes, including celiac disease, gastric *H. pylori* infection, and medication effects, particularly NSAIDs. Correlation with serology is recommended." In cases where there are gastric biopsies that allow the presence or absence of *H. pylori* infection to be assessed, we change the comment appropriately.

Serrated Colorectal Polyps

The spectrum of serrated colorectal polyps includes

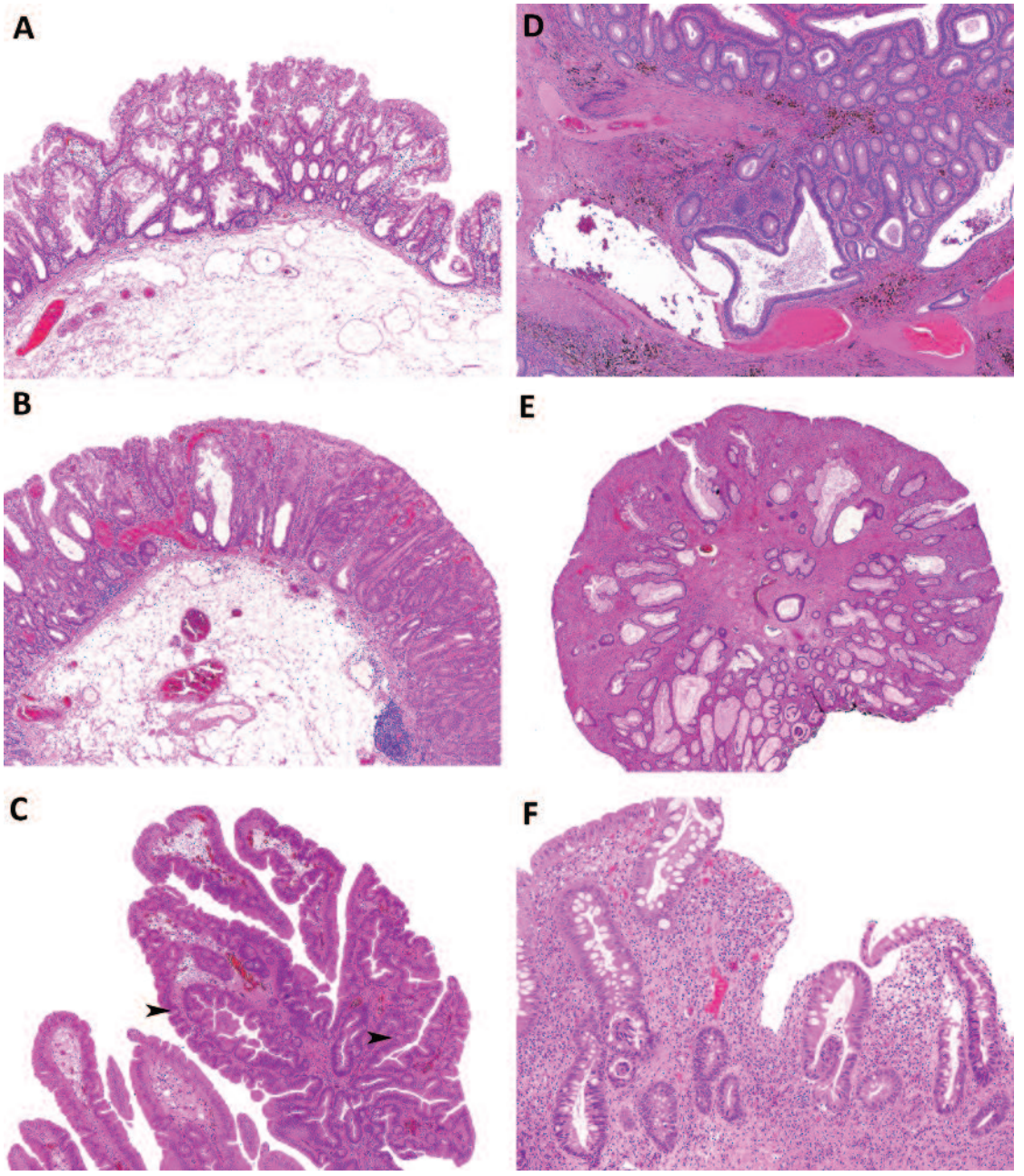


Figure 2. *A*, Sessile serrated adenoma. There are pan-crypt serrations, dilated crypts, boot-shaped crypts, and crypts with inverted T-shapes. *B*, Sessile serrated adenoma with dysplasia. On the left is typical sessile serrated adenoma, whereas on the right, there is dysplasia with an abrupt cutoff between the dysplastic and nondysplastic foci. *C*, Traditional serrated adenoma: an exophytic villous-like lesion with rigid serrations, elongated eosinophilic epithelial cells, and numerous ectopic crypt foci, two of which are indicated by arrowheads. *D*, Part of a tubulovillous adenoma with pseudoinvasion. Herniated mucosa characterized by crypts with surrounding lamina propria and abundant hemosiderin in the background. *E*, Inflammatory myoglandular polyp. These prolapse-related polyps resemble juvenile polyps with distorted crypts and abundant lamina propria, but there is a prominent component of smooth muscle in the background lamina propria. *F*, Colonic mucosa from an ulcerative colitis patient on cyclosporine. There is marked atypia deep in the crypts but the atypical nuclei retain much cytoplasm, are variable one to another and there is maturation to the surface. (Hematoxylin and eosin)

hyperplastic polyps (HPs), sessile serrated adenomas (SSAs), and traditional serrated adenomas (TSAs).[14-17]

HPs are typically left sided, small (less than 5 mm), and often multiple. Serrations are present in the luminal half of the crypt, and the crypts tend to be straight with narrow bases. In the sigmoid colon and rectum, basal crypt distortion with splaying of the muscularis mucosae may occur due to prolapse. In the lower-third to one-half of the crypt, the crypt lining cells appear immature, and proliferative cells and mitoses are seen here but not in the upper halves of the crypt. Crypt endocrine cells are often readily identified, and many HPs have a thickened subepithelial collagen band. Three types of HP have been described: (1) the commonest is the microvesicular type in which the enterocytes contain bubbly cytoplasmic mucin; (2) the second commonest type is the goblet cell type, in which there are few enterocytes and most crypt lining cells are goblet cells; these are more subtle in their appearance, having a lesser degree of serration and surface tufting; and (3) the mucin-poor variant, in which there are fewer goblet cells than normal and little microvesicular mucin; these are rare. It is recommended that the particular type of HP not be reported, but it is important to be aware of the variations so that the lesions can be recognized. In our practice, it has become unusual to diagnose an HP on the right side of the colon, and we would suggest that pathologists be wary of making a diagnosis of HP for any polyp that is larger than 0.5 to 1.0 cm or has a flat, sessile, or otherwise unusual endoscopic appearance, as the polyp is probably an SSA. Cutting deeper levels may reveal an SSA that is initially less than obvious.

SSAs occur throughout the large intestine but are commoner on the right side, where they appear as sessile, flat lesions that may be rather inconspicuous at endoscopy. Polyps are often larger than 1 cm in size and have a characteristic constellation of features. Crypts typically show basal architectural changes, with serrations that span the full length of the crypt; crypt bases are usually dilated or show complex serrated architecture with lateral extensions (boot-shaped crypts) (Figure 2A). Abnormally differentiated cells such as gastric epithelium may be seen in the deeper aspect of crypts. Endocrine cells are typically sparse or absent. There is often fat in the submucosa, and occasional SSAs show foci of nonspecific stromal proliferation within the lamina propria. The cells lining the upper aspects of the crypts may have vesicular nuclei with prominent nucleoli; mitoses may be found. It is possible to find hyperplastic polyp-like foci and traditional serrated adenoma-like foci (eosinophilic, pencillate cells) in an SSA; these are typically focal findings and do not deter us from making the diagnosis of SSA. There are published proposals for minimum diagnostic criteria for SSAs such as the presence of one unequivocal, architecturally distorted, dilated and/or horizontally branched crypt, especially with inverted maturation, or greater than two or three contiguous crypts that demonstrate features of SSA (crypts that are dilated and assume abnormal shapes including L-shapes and inverted T-shapes with prominent serrations at the base of crypts). In our practice, we prefer the former, that is, the presence of one classical crypt being sufficient for a diagnosis of SSA.

The pathologist must exclude dysplasia when examining SSAs. Dysplastic foci may resemble that found in conventional adenomas but are sometimes qualitatively different and more subtle (Figure 2B). The presence of dysplasia indicates that the SSA is advanced, that is, further along the pathway to malignancy than those without dysplasia. Following the Canadian consensus guidelines, we report SSAs without dysplasia as "sessile serrated adenoma; negative for dysplasia and malignancy." We report those with dysplasia as "sessile serrated adenoma with dysplasia (low or high grade); negative for malignancy." SSAs with dysplasia should not be reported as mixed SSA-tubular (or tubulovillous) adenoma (TVA), as these are not mixed polyps but rather advanced SSAs. For advanced SSAs, we would add the comment: "Advanced SSAs (with either low- or high-grade dysplasia) are high-risk premalignant lesions that may have a more rapid transformation to malignancy than conventional adenomas. Complete removal of this polyp is recommended."

TSAs are the most enigmatic of the serrated polyps, and we know the least about them. They are typically exophytic and somewhat villiform lesions that sometimes can be difficult to distinguish from TVAs. TSAs occur more commonly on the left side. A curious but useful diagnostic feature of these lesions, and seen in virtually all examples, are crypt buds that appear as small neocrypts forming within the surface epithelium (Figure 2C). Other features such as

hypereosinophilic cells with elongated, pencillate nuclei are seen in most cases. All TSAs have dysplasia; this can be subtle and mild or more obvious and similar to that seen in other adenomas. There is often a patchwork of typical low-grade dysplasia and hypereosinophilic cells with pencillate nuclei in these lesions. The pathologist must exclude high-grade dysplasia, which, in our practice, has not been encountered frequently. Following the Canadian consensus guidelines, we report TSAs without high-grade dysplasia as "traditional serrated adenoma; negative for high-grade dysplasia and malignancy."

Unfortunately, the spectrum of serrated polyps does not end entirely with the above lesions. Not infrequently, we come across polyps that defy accurate classification. We tend to find these more on the left side, where they are more often exophytic. The differential diagnoses usually include TSA versus TVA, or TSA versus SSA. In such cases, we resort to calling these "serrated adenoma, unclassified" with a description of the various features and possible diagnoses. Hopefully, as we learn more about these polyps, this group will shrink in number.

Pseudoinvasion versus Invasion in Colorectal Adenomas

The differentiation of pseudoinvasion from true invasion in adenomas is a frequent reason for consultation because it can be challenging in nonclassic cases. Typical pseudoinvasion occurs in pedunculated sigmoid colon polyps and is identified by herniation of mucosa into the submucosa. As the process is one of herniation of mucosa, the herniated structures represent adenomatous mucosa and therefore consist of circumscribed groups of crypts with their surrounding lamina propria, rather than naked or haphazardly arranged separate glands, as seen with invasive adenocarcinoma. In addition, the degree of atypia present, that is, grade of dysplasia, within the herniated mucosa should match that within the mucosa proper; it generally should not be of a higher grade or look more atypical. The herniation is due to polyp torsion, which also causes hemorrhage, so this or the presence of hemosiderin-laden macrophages is often identified in the submucosa of these polyps (Figure 2D). There may also be hemorrhage at the polyp surface with erosion and exudate, which is further evidence of mechanical disruption to the polyp's blood supply. Acellular mucin pools due to crypt disruption and liberation of mucin into the surrounding tissue are frequent with pseudoinvasion. Problems arise when these classic features are not all present or when there has been some degree of chronicity to the process, resulting in fibrosis within the submucosa. The fibrosis may isolate single crypts and obscure the lamina propria, resulting in an appearance that suggests true invasion. In such cases, we look carefully for hemosiderin (using a histochemical stain, if necessary) and for remnants of lamina propria around the crypts, which would favour pseudoinvasion. We have observed that cutting several extra levels resolves many initially challenging cases.

Mucosal Prolapse – a Mimic

Mucosal prolapse is significant because it may mimic numerous more important diseases in the large intestine.[18-22] Most importantly, it may mimic colorectal cancer both endoscopically, appearing as an ulcerated or polypoid lesion, and histologically. Although mucosal prolapse occurs most often in the rectosigmoid and may be associated with ostomies, anastomoses, and diverticular disease, we have observed that it may occur anywhere in the large intestine. The histological features of mucosal prolapse include fibromuscular proliferation within the lamina propria, crypt elongation and distortion, variable epithelial serration and regenerative changes, surface erosion, and vascular ectasia. There is often a considerable degree of regenerative epithelial atypia, and this, particularly when combined with a fibromuscular stroma, may mimic invasive adenocarcinoma with desmoplasia. The presence of misplaced glands within the submucosa with associated pools of extruded (but acellular) mucin, as seen with the colitis cystica profunda variant of mucosal prolapse, completes the potential diagnostic trap. Awareness of mucosal prolapse and its variants, recognition of the constellation of characteristic features, and knowledge of the potential associated pitfalls are the best defence against erroneous diagnoses.

On the benign side, mucosal prolapse may show overlapping features with acute ischemic colitis, mainly because repetitive mechanical ischemia plays a likely role in the pathogenesis of prolapse. The term "polypoid mucosal

prolapse" may be used for lesions submitted as polyps. These may be misdiagnosed as adenomatous polyps, again due to the degree of regenerative atypia present in some prolapse lesions. Other erroneous diagnoses that may be rendered when faced with a prolapse polyp include (1) SSA, given that epithelial serration is often seen with mucosal prolapse, (2) hamartomatous polyp (either juvenile or Peutz-Jeghers), given that inflammatory myoglandular polyps (variants of mucosal prolapse found in the rectosigmoid) resemble juvenile polyps, but with prominent stromal smooth muscle proliferation (Figure 2E), and (3) perineurioma or fibroblastic polyp, another rectosigmoid lesion with lamina propria fibroplasia and epithelial serrations.

Finally, it must be remembered that although the problem of prolapse is primarily one of overcalling neoplasia, some neoplastic lesions, especially low rectal adenomas, may be associated with secondary mucosal prolapse changes. If care is not taken in this latter situation, diagnostic errors may range from inflammatory cloacogenic polyp (undercalling of dysplasia) to invasive adenocarcinoma (overcalling of muscularis mucosae or submucosal invasion).

Inflammatory Bowel Disease – Pouches and Stumps

Questions often arise about reporting biopsies of ileal pouches in patients previously diagnosed with ulcerative colitis. The problem is often related to a treating physician's question such as "Query pouchitis?" or "Pouchitis versus Crohn disease?"[23-27] Because performance of an ileal pouch–anal anastomosis is generally (but not always) contraindicated for patients with Crohn's disease, the latter is a loaded question, since reassignment of a diagnosis from ulcerative colitis to Crohn's disease could imply prior diagnostic and/or management errors and also potentially lead to surgical removal of the pouch. Ileal pouches almost always have at least mild inflammation, along with mild villous blunting, which is nonspecific and likely related to changes in the anatomy and intestinal flora.

Pouchitis is an idiopathic clinicopathological condition, generally diagnosed in patients with diarrhea and endoscopic and/or histological evidence of inflammation, which often responds to antibiotics. However, correlation among symptoms, endoscopic findings, and histology is poor. Since pouchitis occurs in up to half the patients with ulcerative colitis, and endoscopists generally biopsy pouches only when something is amiss clinically, it is generally safe to assume that pouch biopsies that appear more than mildly inflamed represent "pouchitis," in the absence of a more specific etiology, for example, *Clostridium difficile* or cytomegalovirus (CMV) infection. The decision as to whether pouchitis requires antibiotic treatment will then depend on correlation with clinical and endoscopic findings. We report pouchitis in a manner similar to how we report inflammatory bowel disease (IBD), including the chronicity and degree of activity of the inflammation. Evidence of chronicity includes villous blunting, crypt distortion, and pseudopyloric metaplasia. The presence of erosions or ulcers may be worth stating explicitly and should always prompt a careful search for CMV inclusions. As an example, "chronic active pouchitis (severe) with ulceration," may be the diagnosis for cases of severe pouchitis. As mentioned above, many pouches will show mild nonspecific inflammatory and architectural changes; we report these descriptively and do not diagnose as "pouchitis."

It is unwise to entertain a diagnosis of Crohn's disease in ileal pouch biopsies from a patient previously diagnosed with ulcerative colitis, as Crohn's-like features, including granulomas and even fistulas, may be seen with pouchitis, although the latter become less common after the first year. When asked to assess for Crohn's disease in this situation, we suggest the comment: "There are no reliable histological criteria for diagnosing Crohn's disease in ileal pouch biopsies from a patient previously diagnosed with ulcerative colitis," in order to inform endoscopists that pouch biopsies performed to find the answer to such a question are invariably unhelpful.

Similar questions often arise about reporting on biopsies from colorectal stumps in patients with IBD. It is generally safe to assume that stump biopsies that appear chronically inflamed represent diversion proctocolitis. Never reassign a previous diagnosis of ulcerative colitis to Crohn's disease based on stump biopsies, since Crohn's-like features may be seen with diversion proctocolitis. When faced with the question "Diversion versus IBD?" we suggest reporting it as "chronic active proctocolitis (mild/moderate/severe)" with the comment: "Although the changes likely represent

diversion proctocolitis, it is not possible to absolutely exclude the possibility of superimposed IBD within biopsies from a colorectal stump."

Inflammatory Bowel Disease – Dysplasia

The challenges related to the recognition of dysplasia in IBD, as well as correct grade assignment, are similar to those described for BE and occur mainly with regard to low-grade dysplasia and cases indefinite for dysplasia.[28-31] An additional confounder in the setting of IBD is drug-related pseudodysplasia. This has been best characterized with cyclosporine therapy but may also be seen with other immunosuppressive agents with antimetabolite action and should especially be considered in patients who have undergone liver transplantation for primary sclerosing cholangitis (Figure 2F).

However, what has become more important for the pathological reporting of dysplasia in IBD is the correct interpretation of the clinical significance of such lesions in the context of their endoscopic or macroscopic appearance. Older patients with IBD may develop sporadic adenomas, which require no further management beyond the routine surveillance schedule, and such a diagnosis may be made in an older patient with a discrete lesion outside the colitic zone. However, lesions in younger patients and/or within the colitic zone are correctly considered to be an IBD-related, dysplasia-associated lesion or mass (i.e., DALM lesions), but it is no longer the case that high-grade dysplasia in any DALM lesion warrants a colectomy. What matters now for an IBD-related dysplastic lesion is whether it is flat dysplasia or raised dysplasia and, in the case of raised dysplasia, whether it is endoscopically "adenoma-like" or not. Flat dysplasia of any grade carries a high risk of associated malignancy. The risk of coincidental cancer with flat low-grade dysplasia is 20% (with a 50% risk of progression to a higher grade lesion), whereas the risk with high-grade dysplasia is greater than 40%. Thus, colectomy should be considered for patients with flat dysplasia, regardless of the grade. In the case of raised dysplasia, the endoscopic appearance of the lesion is paramount. An "adenoma-like" dysplastic lesion is discrete, completely removable by endoscopy, and, by definition, shows no malignancy. Patients with such a lesion, irrespective of the grade of dysplasia, should be followed up in the short term because of frequent polyp recurrence but otherwise may be spared colectomy and managed with surveillance, since the risk of malignancy is no greater than baseline. However, a raised dysplastic lesion that is not discrete or is not readily removable by endoscopy, irrespective of the grade of dysplasia, carries a risk of associated malignancy (occult or visible) of greater than 40%, and a colectomy should then be recommended to the patients.

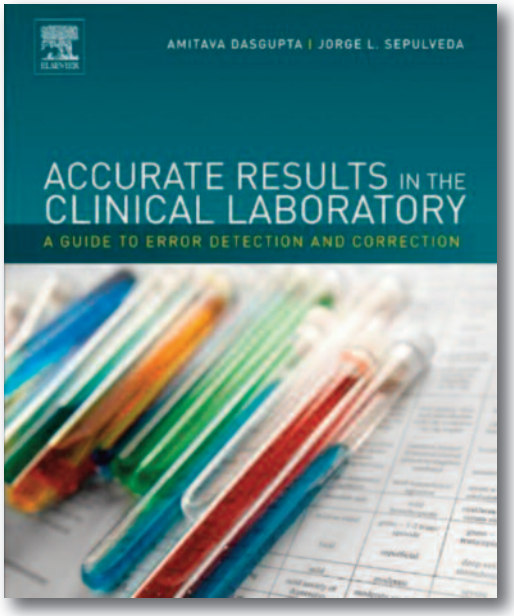
Biopsies of any polypoid lesion should be accompanied by biopsies of the surrounding flat mucosa in order to exclude flat dysplasia. Although it is still recommended that the grade of dysplasia be reported, it is usually not particularly relevant to the management. The endoscopic or macroscopic appearance of what was biopsied, coupled with a definite diagnosis of "dysplasia" should provide the clinician with sufficient information for appropriate management. Further, it is recommended that a second opinion from an expert pathologist be sought to confirm any diagnosis of dysplasia in the setting of IBD, with the exception of an obviously sporadic adenoma. Finally, since the pathologist may not have a reliable description of the endoscopic appearance of such lesions, it may be useful to use the comment: "This biopsy shows (low-grade or high-grade) dysplasia. The appropriate management will depend on the endoscopic appearance of the lesion. Colectomy should be considered in the case of flat dysplasia or raised dysplasia that is not discrete or is not readily removable by endoscopy, given the high risk of associated malignancy."

References

1. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679–92.
2. Maguire A, Sheahan K. Pathology of oesophagitis. Histopathology 2012;60:864–79.
3. Parfitt JR, Gregor JC, Suskin NG, et al. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. Mod Pathol 2006;19:90–6.
4. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7–42.
5. Vietha M, Langnerb C, Neumannc H, Takubod K. Barrett's esophagus. Practical issues for daily routine diagnosis. Pathol Res Pract 2012;208:261–8.
6. Odze RD. What the gastroenterologist needs to know about the histology of Barrett's esophagus. Curr Opin Gastroenterol 2011;27:389–96.
7. Riddell RH, Odze RD. Definition of Barrett 's esophagus: time for a rethink — is intestinal metaplasia dead? Am J Gastroenterol 2009;104:2588–94.

8. Patil DT, Goldblum JR, Rybicki L, et al. Prediction of adenocarcinoma in esophagectomy specimens based upon analysis of preresection biopsies of Barrett esophagus with at least high-grade dysplasia: a comparison of 2 systems. Am J Surg Pathol 2012;36:134–41.
9. Voltaggio L, Montgomery EA, Lam-Himlin D. A clinical and histopathologic focus on Barrett esophagus and Barrett-related dysplasia. Arch Pathol Lab Med 2011;135:1249–60.
10. Maru DM. Barrett's esophagus: diagnostic challenges and recent developments. Ann Diagn Pathol 2009;13:212–21.
11. Lomo LC, Blount PL, Sanchez CA, et al. Crypt dysplasia with surface maturation: a clinical, pathologic, and molecular study of a Barrett's esophagus cohort. Am J Surg Pathol 2006;30:423–35.
12. Hammer STG, Greenson JK. The clinical significance of duodenal lymphocytosis with normal villus architecture. Arch Pathol Lab Med 2013;137:1216–9.
13. Walker MM, Murray JA. An update in the diagnosis of coeliac disease. Histopathology 2011; 59:166–79.
14. Bettington M, Walker N, Clouston A. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology 2013;62:367–86.
15. Driman DK, Marcus VA, Hilsden RJ, Owen DA. Pathological reporting of colorectal polyps: pan-Canadian consensus guidelines. Can J Pathol 2012;4:81–90.
16. Huang CS, Farraye FA, Yang S, O' Brien MJ. The clinical significance of serrated polyps. Am J Gastroenterol 2011;106:229–40.
17. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315–29.
18. Parfitt JR, Shepherd NA. Polypoid mucosal prolapse complicating low rectal adenomas: beware the inflammatory cloacogenic polyp! Histopathology 2008;53:91–6.
19. Singh B, Mortensen NJ, Warren BF. Histopathological mimicry in mucosal prolapse. Histopathology 2007;50:97–102.
20. Ball CG, Dupre MP, Falck V, et al. Sessile serrated polyp mimicry in patients with solitary rectal ulcer syndrome. Is there evidence of preneoplastic change? Arch Pathol Lab Med 2005;129:1037–40.
21. Li SC, Hamilton SR. Malignant tumors in the rectum simulating solitary rectal ulcer syndrome in endoscopic biopsy specimens. Am J Surg Pathol 1998;22:106–12.
22. Groisman GM, Polak-Charcon S, Appelman HD. Fibroblastic polyp of the colon: clinicopathological analysis of 10 cases with emphasis on its common association with serrated crypts. Histopathology 2006;48:431–7.
23. Weber CR, Rubin DT. Chronic pouchitis versus recurrent Crohn's disease: a diagnostic challenge. Dig Dis Sci 2013;58:2748–50.
24. McCurdy JD, Loftus EV, Jr., Tremaine WJ, et al. Cytomegalovirus infection of the ileoanal pouch: clinical characteristics and outcomes. Inflamm Bowel Dis 2013;19:2394–9.
25. Liu ZX, Deroche T, Remzi FH, et al. Transmural inflammation is not pathognomonic for Crohn's disease of the pouch. Surg Endosc 2011;25:3509–17.
26. Navaneethan U, Shen B. Diagnosis and management of pouchitis and ileoanal pouch dysfunction. Curr Gastroenterol Rep 2010;12:485–94.
27. Warren BF, Shepherd NA, Bartolo DC, Bradfield JW. Pathology of the defunctioned rectum in ulcerative colitis. Gut 1993;34:514.
28. Harpaz N, Polydorides AD. Colorectal dysplasia in chronic inflammatory bowel disease: pathology, clinical implications, and pathogenesis. Arch Pathol Lab Med 2010;134:876–95.
29. Ullman T, Odze R, Farraye FA. Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. Inflamm Bowel Dis 2009;15:630–8.
30. Parfitt JR, Driman DK. Pathological effects of drugs on the gastrointestinal tract: a review. Hum Pathol 2007;38:527–36.
31. Hyde GM, Jewell DP, Warren BF. Histological changes associated with the use of intravenous cyclosporin in the treatment of severe ulcerative colitis may mimic dysplasia. Colorectal Dis 2002;4:455–8.

Accurate Results in the Clinical Laboratory: A Guide to Error Detection and Correction



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Laboratories produce important information for clinicians, and a good quality assurance program is expected to be implemented to guarantee accuracy. In *Accurate Results in the Clinical Laboratory: A Guide to Error Detection and Correction*, the quality assurance issues are examined in reverse mode, with the focus on what can go wrong. The reader will not find a systematic approach to implement a quality assurance program here. Rather, the book is intended as a guide to increase the awareness of both clinicians and laboratory professionals with regard to the various sources of errors in laboratory tests and how to minimize them.

The two editors were assisted by 28 experienced contributors from the United States and Canada. One positive aspect of the book is the case studies given throughout the 22 chapters. This makes reading more interesting by highlighting the concepts and the clinical impact of laboratory errors, which may be devastating. The authors not only provide a list of potential errors and interferences but also explain the mechanisms involved. In many cases, errors are related to specific interferences in a particular specimen. Contrary to other textbooks, many chapters are sufficiently detailed to provide discussions of specific errors on a test-by-test basis.

Preanalytical issues are covered in four chapters, and 11 chapters are devoted to chemistry, endocrinology, immunoassays, therapeutic drug monitoring (TDM), drugs of abuse, and tumour markers. TDM and toxicology are especially well covered with many interesting case reports. One chapter focuses on problems with alcohol testing and how to identify false positives or negatives. Another explains the impact of herbal medicines that lead to unexpected laboratory results. Organ toxicity may be the first clue to exposure to herbal medicine.

Hematology, coagulation, and transfusion are discussed in two chapters. Two other chapters are also devoted to challenges in serologic and microbiologic testing. False negative or positives, misidentification of organisms, and errors in antimicrobial susceptibility testing are examined. Issues in molecular biology and pharmacogenomics are developed in two specific chapters. Unfortunately, anatomic pathology is not part of this textbook.

I noticed several minor errors, for example, the listing of hydrogen ions at 40 millimoles per litre (mmol/L) in Table 3.1 "Principal components of plasma". (Hydrogen ion [H+] concentration is 40 nanomoles, one million-fold less, and does not belong in that table). However, the authors have done a good job, as the book is easy to read and quite comprehensive with ample references. Overall, the book is definitely worth reading, as it fulfills its objective of

providing a guide to sources of laboratory errors and how to minimize them. I would recommend it to all professionals involved in laboratory medicine, especially clinical pathologists, medical biochemists, microbiologists, hematopathologists, residents, and their teachers! Error-free laboratory results are essential for patient safety. The book well help laboratory workers develop for the ability to identify and be aware of discordant specimen results. I guess we could call this experience!

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Building the reputation of pathology in Canada

Pathology is at the heart of medical treatment in Canada. Every day, pathologists across the country analyze hundreds of thousands of test results and make critical diagnoses that determine how patients are treated. Yet, research shows that less than 10% of the public understands the role pathologists play in making diagnosis that drive patient treatment and care.

As doctors who work behind the scenes, pathologists have remained largely invisible to the public. A series of incidents of pathology error in recent years have shone a light on the profession, but in the worst way possible. Pathologists are now grappling with significant public scrutiny, worsened by low public awareness and understanding. Insufficient funding, increasing workloads and an inability to recruit enough young, talented doctors add to the challenges. The result is a profession struggling to earn the reputation and respect it deserves.

Public Awareness Levels

Responsibility for Determining Diagnosis From the Lab Test

The doctor who ordered the test	55%
Pathologists	6%

Responsibility for Determining Treatment

The doctor who ordered the test	76%
Pathologists	5%

Changing technology and advances in personalized medicine are opening up new areas for pathologists and innovative ways to improve patient care. In order for pathologists to take proper leadership in these areas, the profession needs to strengthen its reputation and build profile among patients, other medical professionals, government and hospital administration. This begins with building public awareness.

Putting a Face on Pathology

Edelman was engaged to develop recommendations for a public relations campaign aimed at building the reputation of pathology in Canada. Through industry research and various consultations, recommendations for a communications campaign were developed based on the strategy of "Putting a face on pathology".

The goal of the proposed 'MyPathologist.ca' campaign is to identify and personalize pathologists, and elevate their role as important members of a patient's healthcare team. So that as the public, we understand that "my diagnosis and treatment depends on my pathologist".

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