Cytodiagnosis in the Autopsy Suite
A Tool for Improving Autopsy Quality and Resident Education
Vicki J. Schnadig, MD; Claudia P. Molina, MD; Judith F. Aronson, MD

• Context.—Despite several publications attesting to its accuracy and value, cytology is rarely used for preliminary autopsy diagnosis in the United States. Postmortem cytodiagnosis has the potential to increase the accuracy and specificity of the provisional and final autopsy diagnoses, increase resident interest in cytodiagnostics, and direct pathologists to request pertinent special studies, such as microbial cultures and special stains.

Objective.—To assess and illustrate the value of cytodiagnostics for improving autopsy quality assurance and resident education.

Design.—Eighty-five samples were evaluated from 49 nonconsecutive autopsies. Sixty-five focal lesions were sampled by direct scraping. Diffuse lung consolidation was sampled by fine-needle aspiration (20 samples). Smears and cytocentrifuge preparations of fine-needle aspirations were routinely stained by both Papanicolaou and Romanowski methods. Cytologic diagnoses were compared with final autopsy diagnoses, and both cytology and pertinent histology were reviewed.

Results.—Clinical or radiographic antemortem site-specific diagnoses had been made in 28 (33%) of the 85 samples. A definite diagnosis was made by postmortem cytology in 68 (80%) of 85 samples, and these diagnoses could contribute to provisional autopsy diagnosis in 46 instances (68%). Resident and faculty enthusiasm for the use of cytology in the autopsy suite has increased during the 7 years following the study. Case examples illustrating the benefits of postmortem cytology are provided.

Conclusions.—Postmortem cytology benefits both autopsy quality and resident education.

Materials and Methods

Although cytdiagnostic techniques have been reported to provide fast, inexpensive, and accurate autopsy diagnoses,1–4 cytology appears to be a rarely used diagnostic stratagem in US autopsy suites.3,6,7 Two recent publications discussed the declining enthusiasm for autopsy in the United States and the need for increasing the autopsy rate, and the importance of providing high-quality autopsies with rapid result feedback to clinicians.8 The latter should include a more complete provisional report and a preliminary cause of death statement. Descriptive, nondiagnostic terms, such as large necrotic mass, should be avoided in the preliminary autopsy diagnosis (PAD). Rush histology and frozen sections are potential methods of achieving this goal; however, Walker and Going2 have mentioned that necropsy frozen sections are often of poor quality, and several authors have noted that when infectious agents are present, the risk of cryostat contamination is eliminated and aerosol risk is reduced by the use of cytodiagnostics.2–4 Rush histology cannot provide information while the autopsy is being performed. Fine-needle aspiration (FNA) techniques can also be used to sample areas that are not routinely opened at autopsy, such as joint spaces and facial lesions. At our institution, postmortem cytodiagnosis has been used by one of the authors (V.J.S.) for more than 10 years in order to both form more precise PAD and direct more efficient use of microbial culture techniques. In 1999 a formal study was conducted to assess the value of cytology for improving PAD quality. The intent was also to increase faculty interest in autopsy cytology, to advance resident education by introduction of cytology to first year residents, and to provide immediate feedback at gross organ conference. The results of that study and 4 selected cases illustrating the value of cytodiagnostics in the autopsy suite are given here.

Materials and Methods

All samples for this study were collected during 1999, except for one that was collected in the beginning of 2000. Because the intent of the study was to assess the utility of cytologic diagnostic techniques for preliminary diagnosis, the study was limited to autopsies in which there were either focal lesions or diffuse pulmonary consolidation on gross evaluation. These are findings that are amenable to cytodiagnostics evaluation and for which cytology could potentially allow for a specific rather than descriptive PAD. Also, because this study represented our first attempt to formally introduce cytdiagnostic techniques to the autopsy, and because the autopsy faculty was not accustomed to using these techniques, not all autopsies with focal lesions or consolidation had cytologic sampling. Cytodiagnostic techniques were used to evaluate 81 samples taken from 49 nonconsecutive autopsies. In 4 samples, two distinctly different diagnostic conditions were present at the same site; for the sake of analysis we considered each condition as a separate sample, bringing the total sample number to 85. Direct tissue scraping was used to sample focal lesions seen in freshly cut, unfixed tissue. A small amount of scraped tissue was placed near the frosted ends of glass slides, and 2 to...
RESULTS

A total of 65 samples were scraping preparations, and 20 were lung FNAs. Definite cytodiagnoses were made in 68 (80%) of the 85 samples taken from a total of 49 autopsies. Antemortem site-specific diagnoses had been made radiologically or pathologically in 28 (33%) of the 85 samples. A total of 30 samples were placed in the infectious disease category, and definite infectious disease cytodiagnoses were made in 28 (93%) of the 30. Diagnoses correlated with FAD in 27 (96%) of 28. Correct infectious disease cytodiagnoses included 11 diagnoses of bacterial infection, including 5 bronchopneumonia or pleuritis, 1 endocarditis, 1 sepisc splenitis, 1 bacterial cholecystitis, 1 pyelonephritis, 1 psoas abscess, and 1 infected skin papaule. There were 7 fungal cytodiagnoses that concurred with FAD, including 2 cryptococcosis, 2 candidiasis, 2 fungal infections consistent with aspergillosis, and 1 Pneumocystis jiroveci infection. Mycobacterial infections were diagnosed in 5 samples. In a sixth case, a caseating node with stainable organisms was seen in both cytologic and histologic preparations and was interpreted as consistent with nonactive mycobacterial infection (the patient had a history of silicosis and mycobacterial infection and is discussed in detail below). Viral cytopathic effect was seen in 3 cytologic samples, and all were confirmed by histology. Two samples had cytomegalovirus (CMV) cytotoxicologic cell changes, and one sample had both herpes and CMV cytotoxicologic cell changes. In the latter case, CMV changes were found in the histologic sample with difficulty after a focused search for CMV was instigated owing to the prior cytodiagnosis. There were 3 samples for which either a definite diagnosis was not made or the cytodiagnosis did not include the infectious agent. Colon smear from 1 case of pseudomembranous colitis was interpreted as mixed bacteria and neutrophils without a specific diagnosis. In 2 cases, a cytodiagnosis of diffuse alveolar damage was made. In both, invasive pulmonary aspergillosis was seen in histologic sections. In both cases, however, pneumocyte hyperplasia was present, and hyaline membranes (1 case) or intravascular fibrin (1 case) were also seen upon review of lung sections.

There were 27 samples in the neoplasia category, all of which were from patients proven to have neoplastic disease at the sites sampled. A total of 20 (74%) of the 27 yielded cytologic diagnoses, all consistent with the FAD. In 7, cytology findings were nondiagnostic or suspicious. Correct cytodiagnoses included adenocarcinoma or poorly differentiated non–small cell carcinoma (12), small cell carcinoma (1), hepatocellular carcinoma (2), melanoma (1), lymphoma (3), and seminoma (1). Of these 20 malignant diagnoses, 8 represented malignancies not diagnosed antemortem, 7 represented metastases from known primaries that had not been documented antemortem, and 1 represented the primary in a case of carcinomatosis of unknown origin. The latter is described in detail below. Four diagnoses were made from malignancies or metastases with clinical antemortem diagnoses. No diagnosis was made in 7 cases: 1 case of osteoblastic bony metastasis from prostate adenocarcinoma, and 5 lymphomas and 1 osteosarcoma admixed with pleuritis. Necrosis, poor cell preservation, and fibrosis accounted for the nondiagnostic samples.

There were 23 samples derived from miscellaneous benign processes. In 15 (65%) of the 23, definite cytodiag-
nos. were given. A total of 13 (87%) of these 15 diagnoses were compatible with the FAD, and diagnoses included infarcts or fulminant necrosis (6), hepatic steatosis (1), pulmonary aspiration (2), HIV-associated lymphoid depletion with plasmacytosis (1), severe passive hepatic congestion (1), benign lesion consistent focal nodular hepatic hyperplasia (1), and hepatic regenerative nodule (1). There were 2 diagnoses that did not correlate with the FAD. In one case, aspiration was suspected on lung FNA, and scanty foreign material was found in the tracheobronchial tree, without presence of pneumonitis, on review of histology. In another patient, who had a documented medical history of silicosis and atypical mycobacterial infection, abundant ferruginous bodies were identified in FNA of lung, but only silicosis was mentioned in the FAD. Details of the reanalysis of this case are given below. Of the 8 nondiagnostic samples, 3 were considered suspicious for neoplasm but proved to be benign. The changes found histologically were radiation effect, toxic cardiomyopathy in a patient treated for melanoma, and intestinal splenosis. The latter was thought to be suspicious for Kaposi sarcoma by cytology. The remaining 5 nondiagnostic samples had FAD reports of pulmonary congestion (1), splenic congestion (1), pancreatitis (1), lymphoid tissue with sinus histiocytosis and hemophagocytosis (1), and emphysema (1). Cytologic evaluation in these cases contained nonspecific, benign cells not allowing for diagnosis.

In 7 lung FNA samples, lung injury (diffuse alveolar damage or lung injury with fibroin exudate and type II pneumocyte hyperplasia) was diagnosed on the basis of postmortem FNA because of the presence of fibroin material and large, squamous epithelial cells consistent with type II pneumocyte hyperplasia. The latter cells often were seen encircling or in close proximity to the fibroin debris. Two of these cases were ultimately placed in the infectious disease category, owing to the FAD of pulmonary infection (1 invasive aspergillosis and 1 combined bacterial and aspergillus pneumonia). These are discussed above. The remaining 5 cases are categorized as lung injury. Of these 5 cases, 3 had an FAD diagnosis of either diffuse alveolar damage (2) or organizing pneumonia (1). The fourth and fifth had FAD of alveolar hemorrhage and pulmonary edema, respectively; however, hyaline membranes and type II pneumocyte hyperplasia were found on review of both. Assessment of which cytodiagnoses were useful to improve the accuracy of the PAD was made. Diagnoses included as contributory to PAD were those that allowed one to make a specific diagnosis that could only be descriptive without the cytodagnosis. For example, obvious metastases from known malignancies were not considered contributory; however, cytodiagnoses of specific causes of diffuse lung consolidation, such as pneumocystosis or bacterial pneumonia; cytodiagnoses of focal lesions that by gross evaluation could represent infection, infarct or, neoplasm; and cytodiagnoses of previously undiagnosed neoplasms were considered contributory to PAD accuracy.

Of the 68 definite diagnoses made, 46 (68%) were considered contributory to PAD accuracy. A summary of our results is given in Table 1.

The following illustrated cases, all from the study, demonstrate examples of the impact of cytodiagnosis in the autopsy suite.

**Case 1**

A 49-year-old woman died shortly after total hysterectomy and bilateral oophorectomy for disease clinically interpreted as ovarian carcinoma but which was reported after surgical pathology evaluation as adenocarcinoma, metastatic to ovaries, uterus, and omentum. The patient died shortly after surgery without antemortem identification of her primary. Autopsy confirmed widespread peritoneal carcinomatosis. Also noted was a thickened gallbladder containing numerous stones and thick, cloudy exudate. Initial impression of the gross findings by the faculty prossector was acute and chronic cholecystitis and cholelithiasis. A smear preparation of the exudate contained abundant neoplastic cells consistent with adenocarcinoma and compatible with gallbladder primary. Significant inflammation was not seen. This cytodiagnosis was given to the prossector during the gross dissection. This information focused the prossector’s attention to the gallbladder as a potential primary and motivated her to take multiple sections of the gallbladder. Figure 1 illustrates autopsy findings. The gross appearance of the gallbladder is seen in Figure 1, A, and the cytologic preparations and their histologic correlates are seen in Figure 1, B through E.

**Cases 2 and 3**

These cases illustrate the use of cytology in providing a specific diagnosis for pseudomembranous and ulcerative esophagitis. A 57-year-old man died with antemortem diagnosis of multiple myeloma treated with high-dose chemotherapy. At autopsy, pseudomembranous esophagitis (Figure 2, A) and proctitis were found. Scrapings of both esophagus (Figure 2, B) and rectum were done, and candidiasis was diagnosed. Invasive candidiasis involving the gastrointestinal tract, tracheobronchial tree, and lungs, was confirmed by histology. A 24-year-old man with a history of AIDS died of respiratory failure. Autopsy disclosed numerous esophageal ulcers with raised, yellow borders. Scraping of the esophageal lesions revealed squamous cells, many of which had herpesvirus cytopathic effect (Figure 2, C). Focally, there were a few cuboidal cells with CMV cytopathic effect (Figure 2, D). Postmortem lung FNA from the same case contained abundant cells with CMV cytopathic effect. Herpes esophagitis with focal CMV esophageal vasculitis, and CMV pneumonitis were confirmed by histology. Cytomegalovirus changes were found very focally within the esophageal submucosal vessels after focused search based on the cytologic findings. Only one convincing inclusion was seen in esophagus sections. This was confirmed by immunostain.
Figure 1.  
A, Gallbladder and inferior surface of liver. Gallbladder wall is markedly thickened and contains abundant stones. Turbid, anchovy-colored fluid is seen in the lower portion of gallbladder lumen. B, Smear preparation of fluid demonstrates presence of neoplastic columnar cells (Papanicolaou stain, original magnification ×320). C, Histologic section of gallbladder wall shows an area of moderately differentiated adenocarcinoma in situ (hematoxylin-eosin, original magnification ×120). Note that neoplastic columnar cells in this section resemble the cells seen in panel B.  
D, Undifferentiated malignant cell is seen in smear preparation of gallbladder fluid (Papanicolaou stain, original magnification ×840). E, Section shows presence of very poorly differentiated neoplastic cells infiltrating wall of the gallbladder. The cells in this section resemble the cell seen in panel D (hematoxylin-eosin, original magnification ×240).

Figure 2.  
A, Longitudinally opened esophagus with presence of pseudomembranous exudate diffusely involving the mucosa. B, Smear preparation of exudate contains abundant budding yeast forms and pseudohyphae consistent with Candida sp (Romanowski stain, original magnification ×1100). C, Smear preparation of a different esophagus in the study, which had ulcerative esophagitis. A multinucleated cell with margination of chromatin and intranuclear inclusions typical of herpesvirus cytopathic effect is seen (Papanicolaou stain, original magnification ×1100). D, Cell with cytomegalovirus cytopathic change is also seen in the same smear preparation as in panel C (Papanicolaou stain, original magnification ×1100).

Case 4

A 65-year-old man with both a known history of silicosis that was diagnosed more than 20 years prior to death and a recent history of atypical myobacterial infection died suddenly while hospitalized for hip pain. According to his medical records, he had an occupational history of employment as a sandblaster. No mention of other occupational exposure was found in his medical record. Chest
radiographs performed within the last 2 years preceding death showed presence of multiple, bilateral pulmonary nodules, interstitial fibrosis, and calcified mediastinal lymph nodes. At autopsy, numerous firm, calcified nodules were found throughout both lungs. Focal, small areas of caseous necrosis were also seen. Postmortem smear of caseous nodule showed only necrosis with no acid-fast bacilli seen. Fine-needle aspiration of lung revealed abundant ferruginous bodies with thin, central cores (Figure 3, A and B). Histologic sections of lung showed circumscribed nodules composed of concentric layers of hyalinized collagen lacking central pigmentation. Scanty polarizable material consistent with silica was described within some of the nodules. Nodules composed of concentric layers of hyalinized collagen were also found within mediastinal and peribronchial lymph nodes. Also noted were foci of acute pneumonia and fibrocaseous nodules consistent with healed mycobacterial infection. No agreement was reached as to the significance of the ferruginous bodies at the time of autopsy in regard to their clinical significance or whether they represented asbestos fibers or another type of fiber. Although iron stain was performed on one lung section (left apex) at the time of autopsy, the prossector did not note presence of ferruginous bodies.

Prior to preparation of this manuscript, this case was again reviewed. At that time only one lung block, from the left lower lobe, was available. Hematoxylin-eosin-stained and iron-stained sections were prepared from this block. Rare ferruginous bodies were found in this section (Figure 3, C). The left lower lobe sections (hematoxylin-eosin and iron stains) were then reviewed in consultation with one of the pulmonary pathologists at our institution. It was the consultant’s opinion that there was lower lobe peribroncholar fibrosis with presence of carbon pigment-laden macrophages, and that these findings, along with the presence of ferruginous bodies, were consistent with asbestososis (Figure 3, D). A single collagenized nodule, consistent with the previous diagnosis of silicosis, was also present in this section.

**Cases 5 and 6**

Figure 4 illustrates the lung FNA findings from 2 cases of diffuse pulmonary consolidation. One patient, a 34-year-old man with AIDS, died in hospice without any recent diagnostic studies. Fine-needle aspiration of lung showed abundant *P jiroveci*, which was confirmed by histology (Figure 4, A and B). The other patient was a 16-month-old infant who died 6 days following inhalation

**Figure 3.** A and B, Lung fine-needle aspiration from a patient with history of silicosis. Ferruginous bodies with slender central cores are seen (Romanowsk stain, original magnifications ×500 [A] and ×1250 [B]). C, Lung section shows presence of pigment-laden macrophages and an iron stain-positive ferruginous body (Prussian blue, original magnification ×600). D, Hematoxylin-eosin–stained section of left lower lobe of lung with peribroncholar fibrosis and presence of pigment-laden macrophages (hematoxylin-eosin, original magnification ×100). Inset demonstrates presence of a portion of ferruginous body. These were very infrequent in histologic sections (hematoxylin-eosin, original magnification ×1000).
burn injury. Fine-needle aspiration showed granular and fibrinous debris and presence of large epithelial cells consistent with hyperplastic type II pneumocytes. Findings in this case were clinically consistent with diffuse alveolar damage (DAD), and cytology supported presence of proliferative stage of DAD (Figure 4, C and D).

**COMMENT**

The results of this study indicate that cytology is an accurate method for generating more specific PAD, and thus improving autopsy quality. The study was intended not only to demonstrate that cytodiagnostics techniques are useful to generating high-quality autopsies with more accurate PAD, but to introduce cytodiagnostics methodology to residents and autopsy faculty. The work represented an introduction to methodology not universally used in autopsy pathology. Because there were approximately 10 pathologists of differing backgrounds staffing our autopsy division, there was variation in both use and acceptance of cytodiagnostics techniques and diagnoses, respectively. Also, during the study period there were several different residents working the autopsy service. Although use of cytodiagnostics techniques was limited to focal lesions and lung consolidation, there was no attempt to select for lesions that are more diagnosable by cytology. Owing to faculty and resident variability, not all autopsies with focal lesions or lung consolidation had cytodiagnostics samples taken. These limits to the study were, in our opinion, unavoidable. Of course, many autopsies did not warrant cytodiagnostics methodology. Autopsies without focal lesions or lung consolidation, such as cases with only atherosclerotic cardiovascular disease, myocardial infarction, hypertension, or pulmonary embolism, are examples of cases for which cytology is unnecessary.

Cytodiagnosis is not used for all autopsies at our institution. During the 7 years that followed this study, interest and acceptance of cytodiagnostics techniques has increased among the faculty. Our residents and the pathologist assistant have become enthusiastic about the use of these techniques to help with both formation of the PAD and to determine need for ancillary techniques, such as culture or special staining.

Photomicrographic images of cytologic samples are currently being used for resident teaching, morbidity and

**Figure 4.** A, Cytology preparation of lung fine-needle aspiration (FNA). Intracystic and extracystic organisms typical of *P jiroveci* are seen in FNA preparation (Romanowski stain, original magnification ×1300). B, Lung section from same case as shown in panel A. Typical intra-alveolar *Pneumocystis* “foamy exudate” (hematoxylin-eosin, original magnification ×100). C, Cytology preparation of lung FNA. Enlarged pneumocytes surrounding fibrinous debris (Papanicolaou stain, original magnification ×1000). D, In lung section from the same case as shown in panel D there are type II pneumocyte hyperplasia and hyaline membranes (hematoxylin-eosin, original magnification ×200).
mortality conferences, and other intradepartmental and extradepartmental conferences. Our data indicate that autopsy cytdiagnoses have a reasonable degree of accuracy and can be used to generate more specific PAD, thus improving autopsy quality. Additional benefits include immediate feedback at gross conference and introduction of cytologic techniques to first-year residents. We have demonstrated that autopsy cytology can be used to establish a preliminary diagnosis of previously undiagnosed malignancies, confirm metastases of known primary malignancies, or establish presence of a second primary. It can also be used to distinguish between infection and malignancy.

We have found that most lesions, including the majority of infections, can be provisionally diagnosed using a combination of Papanicolaou and Romanowski stains. *Pneumocystis*, bacteria, *Candida* sp, and *Cryptococcus neoformans* stain well by Romanowski method, and often these organisms can be seen by Papanicolaou stain as well. Papanicolaou stain is an excellent preparation for the detection of fungi and/or the presence of refractile, red bacilli.12,13 When mycobacterial infection is suspected, based on presence of caseation or bacilli on Romanowski stain, confirmatory acid-fast stain is usually performed on the cytologic material. Preparation of a cold, Kinyoun acid-fast stain requires only about 10 minutes. In our cytopathology laboratory, special microbial stains for autopsies are typically done with runs of special stains performed on clinical samples; nonetheless, the autopsy cytology special stains can usually be finished before release of the PAD on the day following the autopsy. We can, however, prioritize simple stains, such as Kinyoun acid-fast and Gram stains, if results are needed in order to provide information to the prosectors during the autopsy. Providing rapid results in cases of microbial infections is useful to inform prosectors whether or not potentially transmissible infectious agents, such as mycobacteria, are present. Results can also guide prosectors in their decision to culture tissue for microbes. At our institution, where there are many diagnostic procedures performed on immunosuppressed patients, special infectious disease stains are performed routinely within the cytology laboratory almost on a daily basis; therefore, addition of an autopsy sample to the run of infectious disease stains does not interfere with the workflow. Microbiology laboratories also could also perform rapid, intra-autopsy stains on smear preparations. Routine stains can be used to provisionally diagnose neoplastic diseases and benign conditions, such as infarcts and stasis. Pulmonary alveolar injury, usually representing either DAD or organizing pneumonia with intra-alveolar fibrin, can be suspected on the basis of seeing hyperplastic pneumocytes and fibrinoid debris in an FNA from a diffusely consolidated lung. In our experience, large, squamoid cells surrounding or closely associated with fibrous and granular material (Figure 4, C and D) have correlated with presence of either the proliferative phase of DAD or organizing pneumonia with the presence of type II pneumocyte hyperplasia and intra-alveolar fibrin. In 1997, one of the authors (V.J.S.) performed postmortem FNA on lung samples, and electron microscopy was performed on aspirates from two cases with cytologic findings suggestive of type II pneumocyte hyperplasia (unpublished data). Electron microscopy from the two FNA samples demonstrated cells with intracytoplasmic myelin whirs typical of type II pneumocytes. We have seen similar cells either encircling or closely associated with fibrin in bronchoalveolar lavage samples from patients with clinical evidence of acute respiratory distress syndrome.

Intra-autopsy evaluation of lesions can lead to appropriate use of cultures, and FNA can be used to sample lesions on the face or within joint spaces. Recently, we used postmortem cytology to diagnose and appropriately culture an unsuspected case of *Histoplasma* endocarditis, and FNA was used to sample a bacterial abscess of the parotid gland in the same patient.14 We have used postmortem FNA to diagnose and culture septic arthritis and have used FNA and polarization microscopy to confirm presence uric acid crystals in a patient with gout. A smear-based provisional diagnosis of glioma was used recently to reassure a clinician that his patient, who died just before admission for a diagnostic procedure, did not have an unrecognized infection or lymphoma.

Successful use of cytology for autopsy diagnosis requires experienced cytopathologists and interest in autopsy cytdiagnosis. It also requires motivation on the part of the prosector and careful correlation of cytdiagnoses with final histologic findings and cultures. While we are not advocating replacing standard histologic methods with cytology, our experience suggests that cytology can be used as an ancillary technique to improve autopsy quality. Cytology helps accomplish some of the goals recommended by Sinard and Blood for providing high-quality autopsies with rapid feedback to clinicians. It also is a valuable teaching tool for residents.

The authors thank Claudia Y. Castro, MD, for providing consultative assistance during review of selected lung sections.

References