Detection of Malignancy in Body Fluids
A Comparison of the Hematology and Cytology Laboratories

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• Context.—Body fluids submitted to the hematology laboratory for cell counts may also be examined for the presence of malignancy. Previous studies evaluating the hematology laboratory’s performance at detecting malignancy in body fluids have reached conflicting conclusions.

Objective.—To investigate the hematology laboratory’s ability to detect malignancy in body fluids by comparison with cytology.

Design.—Retrospective analysis of 414 body fluid samples during an 18-month period, with introduction of new quality assurance measures after the first 210 cases. If no concurrent cytology was ordered, results were compared with recent previous and/or subsequent cytologic, histologic, or flow cytometric diagnoses.

Results.—Of the initial 210 cases, the hematology laboratory detected 3 of 13 malignancies diagnosed by concurrent cytology (23% sensitivity), with no false-positives (100% specificity). Malignancy was not identified on retrospective review of the hematology slides in the 10 discrepant cases. After the initial study, educational sessions on morphology for the medical technologists and a more thorough hematology-cytology correlation policy were implemented. The subsequent 204 hematology laboratory cases had increased sensitivity for the detection of malignancy (60%; 6 of 10). Definitive features of malignancy were seen in only one discrepant hematology laboratory slide on retrospective review. This case had not been flagged for hematopathologist review. None of the discrepancies before or after implementation of the additional quality assurance measures impacted patient care.

Conclusions.—Body fluid processing by the hematology laboratory is not optimized for the detection of malignancy. Concurrent cytologic examination is critical for the detection of malignancy, and needs to be considered as cost-saving measures are increasingly implemented.


Body fluid specimens are submitted to the hematology laboratory primarily for cell counting. In many cases, they are also examined for the presence of malignancy. The cytology laboratory likewise examines body fluids for the presence of malignancy, but not all body fluids are sent to both the hematology and cytology laboratories for evaluation.

Cytology is able to diagnose 70% or more of metastatic carcinoma in malignant pleural effusions when cytologic smears and cell blocks are examined.1 The diagnostic yield of cytology is thought to depend on the skill of the pathologist and type of tumor,2 with lower sensitivities seen in lymphomas (25%–50%), sarcomas (25%), and mesotheliomas (10%).3 Additional thoracenteses may improve the diagnostic yield.3 For ascites fluid, cytology is 40% to 65% sensitive at detecting malignancy, and sensitivity increases to more than 95% in carcinomatosis.4 However, carcinomatosis accounts for only two-thirds of malignant peritoneal effusions.

A perceived benefit of body fluid morphologic examination in the hematology laboratory is earlier reporting of negative results. Many hematology laboratories operate 24 hours a day, and medical technologists are able to report results without mandatory pathologist review. The decision to consult the pathologist is left to the medical technologist’s discretion. In cytology laboratories, all nongynecologic samples, including all body fluids, are personally evaluated by a pathologist as dictated by the Clinical Laboratory Improvement Amendments of 1988. Body fluids are considered diagnostic rather than screening-type specimens in cytology. Thus, whereas a negative screening Papanicolaou test can be signed out by a cytotechnologist, body fluids sent to cytology can be signed out only by a pathologist.

We queried whether the triage of body fluids to hematology versus cytology affected the rate of malignancy detection. Similar comparative studies reported previously have arrived at conflicting conclusions.5,6

METHODS
Study Design
A retrospective quality assurance study of the hematology laboratory at our institution was performed. The study assessed...
the laboratory’s ability to accurately diagnose malignancy in body fluid samples primarily by comparing hematology results with concurrent cytology results.

Data were collected on 414 body fluids submitted to the hematology laboratory during an 18-month period. These included peritoneal, pleural, mediastinal, joint, cerebrospinal, and other miscellaneous fluid specimens. Two groups of consecutive cases (210 and 204, respectively) were evaluated separately in a 2-phase study aimed at assessing the laboratory’s performance before and after additional quality assurance measures were taken. All attending hematopathologists on that service were represented. The body site, diagnosis (malignancy present versus absent), and reporting individual (medical technologist versus hematopathologist) were recorded for each body fluid result. Information was gathered on any available concurrent cytology specimens or, if cytology had not been ordered, any recent previous or subsequent cytology, histology, and/or flow cytometric reports on specimens from the same body site (Table 1).

Quality Assurance

Analysis of the preliminary data from the first group of cases (210) revealed some discrepancies, wherein the hematology laboratory had reported a result of negative for malignancy but concurrent cytology was positive (see “Results”). The negative results had been variably signed out by either medical technologists or hematopathologists. The discrepant slides were then retrospectively reviewed to determine whether malignancy present on the cytology slides was present on the hematology slides. The Romanowsky-, Diff-Quik–, and Papanicolaou-stained slides from the hematology and cytology laboratories were retrospectively reviewed by an experienced hematopathologist and a senior cytopathologist.

The preliminary findings of the initial phase of the study prompted a 2-fold plan for additional quality assurance: an attending hematopathologist would provide education in cellular morphology to the medical technologists, and a more thorough hematology-cytology correlation policy would be implemented.

Education Component.—Eighty cases from the first phase of the study were flagged by the medical technologist for hematopathologist review. A majority of these were interpreted by the hematopathologist as benign. These results indicated that education in cell morphology for the hematology laboratory’s technologists might increase the sensitivity and specificity of the technologists for identifying malignancy in body fluids, and led to the development of an educational component for the quality assurance plan.

Improved Correlation Policy.—The existing hematology-cytology correlation policy was a cross-check performed by the hematopathologist on select cases at his or her discretion. A new, more thorough policy was implemented that required a cross-check on all cases flagged by the medical technologists for pathologist review. If a cross-check showed that concurrent cytology had been ordered and that the result was positive, but if the hematopathologist saw no malignancy on the hematology slide, then the hematopathologist reported the negative body fluid result with a reference to the positive cytology by accession number. Also, in cases where the hematology slide was concerning for malignancy but concurrent cytology had not been ordered, the hematopathologist contacted the treating physician to discuss whether cytology was indicated by the patient’s clinical picture.

RESULTS

The results of the evaluations on body fluids sent to the hematology laboratory were compared with results on concurrent samples sent to the cytology laboratory. If concurrent cytology was not ordered, hematology results were compared with recent, previous, or subsequent cytologic, histologic, or flow cytometric diagnoses (Table 1).

Table 1. Body Fluids Evaluated in the Hematopathology Laboratory and Related Concurrent or Recent Tests

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Phase 1 (n = 210)</th>
<th>Phase 2 (n = 204)</th>
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<tbody>
<tr>
<td>Concurrent cytology</td>
<td>91 (43.3)</td>
<td>76 (37.3)</td>
</tr>
<tr>
<td>Flow cytometry, surgical</td>
<td>60 (28.6)</td>
<td>57 (27.9)</td>
</tr>
<tr>
<td>pathology, or previous/follow-up cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology specimen only</td>
<td>59 (28.1)</td>
<td>71 (34.8)</td>
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</tbody>
</table>

Phase 1

Of the 210 body fluids that were submitted to the hematology laboratory before the implementation of additional quality assurance measures, 107 were peritoneal (51%), 64 pleural (30%), 25 joint (12%), 12 cerebrospinal (6%), and 2 miscellaneous fluids (1%). Ninety-one of the cases (43%) had concurrent cytology ordered; 60 (29%) had a previous and/or subsequent specimen sent to the cytology, surgical pathology, or flow cytometry laboratories; and 59 (28%) were sent only to the hematology laboratory (Figure 1). A majority of the body fluid results (130 specimens; 62%) were reported by a medical technologist, and 80 (38%) were flagged for consultation by the hematopathologist (Table 2).

Of the 91 fluids with concurrent cytology ordered, 13 cases (14%) were diagnosed as malignant by cytology. The hematology laboratory detected only 3 of the 13 malignancies (sensitivity 23%). A medical technologist had consulted the hematopathologist in all 3 cases of concordant malignant results. Of the 10 discrepant malignant cases, a medical technologist had consulted the hematopathologist to review 7 of the cases. The other 3 discrepant malignant cases had not been flagged by a medical technologist for hematopathologist review.

An experienced hematopathologist and a senior cytopathologist retrospectively reviewed the discrepant malignant cases. Diagnostic features of malignancy were not seen in any of the hematology body fluid slides for these 10 cases.

Phase 2

Of the 204 body fluid samples submitted to the hematology laboratory after implementation of the additional quality assurance measures, 104 were peritoneal (51%), 61 pleural (30%), 32 joint (16%), and 7 miscellaneous fluids (3%). Seventy-six (37%) of the cases had concurrent cytology ordered; 57 (28%) had a previous and/or subsequent specimen sent to the cytology, surgical pathology, or the flow cytometry laboratories; and 71 (35%) were sent only to the hematology laboratory (Figure 2).

A majority of the body fluids were reported by medical technologists (169 specimens; 83%; Table 2), an increase over the first phase (62%). The proportion of cases flagged for review by the hematopathologist fell by more than half, from 38% to 17%. The decrease was thought to be due to the in-service education on cell morphology that the technologists received.

Of the 76 fluid samples in phase 2 with concurrent cytology ordered, 10 (13%) were interpreted as positive for malignancy on cytologic examination. The hematology laboratory detected 6 of these malignancies, an increase in sensitivity from 23% in phase 1 to 60% in phase 2. A medical technologist had not consulted the hematopathol-
ogist in the 4 discrepant malignant cases. The discrepancies were retrospectively reviewed by the same expert hematopathologist and senior cytopathologist. Only one diagnostic false-negative result was found to have been reported by the hematology laboratory. The hematology slides for the other cases did not have diagnostic features of malignancy.

Recent (Nonconcurrent) Cytology, Surgical Pathology, and Flow Cytometry Specimens

Sixty cases in phase 1 and 57 cases in phase 2 did not have concurrent cytology, but did have recent (within 2 weeks) cytologic, surgical pathology, or flow cytometry specimen results for comparison. Of the 60 such cases in phase 1, there was one discrepancy identified by the study’s criteria. However, the malignancy identified in the previous peritoneal fluid was likely no longer present in the current peritoneal fluid because of excision of an umbilical mass with metastatic adenocarcinoma.

The 57 such cases in phase 2 included 2 with diagnostic discrepancies. One of the patients with discrepant fluid results had pancreatic adenocarcinoma with carcinomatosis. The other had pancreatic adenocarcinoma and a history of hepatocellular carcinoma, status post liver transplant in 2010. Both body fluids were reported as negative by medical technologists without request for hematopathologist consultation. For both cases, rare, atypical cells suspicious for malignancy were seen on subsequent cytologic specimens. Neither of the corresponding hematology body fluid slides had diagnostic features of malignancy noted on retrospective review by the hematopathologist and cytopathologist.

Clinical Impact

The electronic medical records for the 17 discrepant cases were reviewed for evidence of possible adverse outcomes on patient care. In all cases, there was already a known history of malignancy/metastasis, or a very high clinical suspicion for it. None of the discrepancies had an evident impact on patient care.

Examples of Concurrent Evaluations

Figure 3, A through D, shows 2 body fluids with concordant concurrent results. Figure 4, A and B, shows an
example of discrepant concurrent pleural fluid results. The patient with the latter discrepant fluid results had a history of perforated rectosigmoid adenocarcinoma. Cytologic preparations of a subsequent pleural fluid specimen showed positive immunohistochemical staining for cytokeratin 20, compatible with metastasis from a colorectal primary. No malignancy was seen on the hematology body fluid slide, even on retrospective review. The discrepancy is likely related to differences in laboratory processing (see “Comment”).

Figure 5, A through D, shows 2 body fluids with difficult-to-interpret cytology. The patient whose peritoneal fluid is illustrated in Figure 5, A and B, had stage IV pancreatic adenocarcinoma, with malignant ascites that had been diagnosed the previous month. The patient associated with the pleural fluid in Figure 5, C and D, had a primary pulmonary adenocarcinoma. A malignant pleural effusion positive for TTF-1 and napsin A had been diagnosed 5 months earlier.

Figure 6, A and B, shows the only diagnostic false-negative body fluid result reported by the hematology laboratory in this study. The patient had a history of diffuse large B-cell lymphoma diagnosed 8 months prior to admission. Diagnostic features of malignancy were noted on retrospective review of the pleural fluid slide prepared in the hematology laboratory. The hematopathologist had not been consulted on the case at the time of case sign-out.

**COMMENT**

Detecting malignancy in body fluids poses many challenges. This study aimed to characterize the impact of specimen triage to hematology versus cytology on the rate of detection of malignancy. Previous comparative studies of the hematology and cytology laboratories’ ability to detect malignancy demonstrated sensitivities of the hematology laboratory ranging from 24% to 64.9%, with the studies arriving at conflicting conclusions.

Our initial results confirmed a low rate of malignancy detection by morphologic examination in the hematology laboratory. The absence of diagnostic features of malignancy on retrospective review of the body fluid slides prepared in the hematology laboratory suggested that differences in specimen processing between the 2 laboratories may contribute to the discrepancies. The hematology laboratory uses a single Romanowsky-stained cytospin preparation for cell counting and morphologic review. Also, the cytospin is optimized for cell counting, with fewer cells present on each slide.

In contrast, the cytology laboratory uses multiple slides for the examination of body fluid samples, both air-dried, Romanowsky- (Diff-Quik–) stained and alcohol-fixed, Papanicolaou-stained preparations. The cytospin used by cytology places a greater number of cells on each slide, which increases sampling. The Papanicolaou stain is particularly effective at highlighting nuclear features,
Figure 3. Pleural fluid interpreted as negative for malignancy by the hematology medical technologist (A) and cytopathologist (B). Peritoneal fluid interpreted as positive for malignancy by the hematopathologist (C) and cytopathologist (D) (Romanowsky, original magnifications ×10 [A and C]; Papanicolaou, original magnifications ×10 [B and D]).

Figure 4. Pleural fluid reported negative for malignancy by the hematopathologist (A) and positive for malignancy by the cytopathologist (B). No malignancy was seen on the hematology slide on retrospective review (Romanowsky, original magnification ×10 [A]; Papanicolaou, original magnification ×10 [B]).
Figure 5. Peritoneal fluid interpreted as negative for malignancy by the medical technologist (A) and suspicious for malignancy by the cytopathologist (B). Peritoneal fluid interpreted as negative for malignancy by the medical technologist (C) and positive for malignancy by the cytopathologist (D) (Romanowsky, original magnifications ×10 [A] and ×40 [C]; Papanicolaou, original magnifications ×10 [B] and ×40 [B inset and D]).

Figure 6. Pleural fluid interpreted as negative for malignancy by the medical technologist (A) and positive for malignancy by the cytopathologist (B). Retrospective review by a hematopathologist was interpreted as positive for malignancy in the hematology specimen (Romanowsky, original magnification ×10 [A]; Papanicolaou, original magnification ×10 [B]).
whereas the Romanowsky stain is not. The cytology laboratory is able to make cell blocks that can be used for immunohistochemistry, molecular, and other studies that further increase sensitivity for the detection of malignancy. Finally, all nongynecologic specimens received in the cytology laboratory are evaluated and interpreted by a pathologist.

CONCLUSIONS

Cytologic evaluation is superior to examination in the hematology laboratory for the detection of malignancy in body fluids. Cytology, although not 100% sensitive, uses processing that is optimized for the detection of malignancy. The discrepancies in detection of malignancy identified in this study and the lower sensitivity of the hematology laboratory most likely represent sampling variances due to processing differences, rather than variances in diagnostic skills among pathologists. The additional quality assurance measures implemented during this study were not aimed at improving the hematology laboratory’s ability to detect malignancy, but at facilitating specimen triage to the cytology laboratory where the detection of malignancy in body fluid specimens is maximized.

The hematology laboratory’s processing of body fluid specimens is optimized for cell counting, not for the identification of malignancy. If morphology is concerning for malignancy, the pathologist should discuss triage of the hematology specimen with the ordering physician if cytology has not been concurrently ordered. In the current era of avoiding duplicate testing, and with growing pressure on physicians to reduce testing in general, cytologic examination should not be sacrificed in the interest of cost containment.

References