

Special Articles

THE CASE FOR EXFOLIATIVE CYTOLOGY OF SEROUS EFFUSIONS

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DESPITE a world-wide surge of interest in the cytological detection of cancer, uncertainty about the usefulness of searching for cancer cells in serous effusions still lingers, and this feeling seems strong in Britain, where exfoliative cytology is gaining rather tardy acceptance. In fact, one British laboratory's poor results with the exfoliative cytology of serous fluids have been adduced to question the reliability of exfoliative cancer cytology in general.¹ Our experience has convinced us that cytological examination of serous effusions is worthwhile, and not too difficult or complex for inclusion in the routine of a busy pathological laboratory.

In 1957, a laboratory of exfoliative cytology was set up within the department of pathology of the University of Michigan. During its first six years we examined 695 pleural, 224 peritoneal, and 16 pericardial fluids—a total of 935 specimens from 634 patients. We have reviewed the records of all these cases and assessed the results of the exfoliative cytology of the effusions in the light of the final clinical diagnoses.

METHOD

Each fluid was centrifuged as soon as it was received in the laboratory, and the cellular deposits were smeared on slides with a bacteriological loop. Before the slightest trace of drying occurred, the smears were fixed by immersion in 95% ethyl alcohol until they could be stained by the Papanicolaou method. In addition to these permanent preparations, a stained wet-film was prepared by mixing a drop of serum toluidine-blue stain with a drop of the cellular deposit.² This wet-film was ready for examination immediately.

RESULTS

There were two groups of patients: those with and those without cancer. In most of the cancer cases there was histopathological evidence of neoplasm, but when this was not so, the evidence for malignant neoplasm was either clinical or radiological, or both. The final picture never left any doubt about the neoplastic nature of the disease.

Nearly all examinations were reported to be either "negative" or "positive" for cancer cells; and when positive we gave an opinion about the type of cell composing the neoplasm. We wish to emphasise, at this point, that positive reports were expressed with decisiveness, and only occasionally had we to fall back on reporting a degree of suspicion. For statistical analysis, however, any "suspicious" reports have been regarded as negative. The justification for this is that we found the clinicians were compelled, for practical purposes, to regard reports which were not definitely positive as tantamount to negative. Of the 935 reports, 283 were positive, 616 negative, and 36 suspicious.

The accuracy of the cytological reports for all cases was:

	No. of patients	Positive cytology	Negative cytology
With cancer	401	217	184
Without cancer .. .	233	2	231
Total	634	219	415

and for the various types of cancer it was:

	No. of cases	Positive cytology	Negative cytology
Adenocarcinoma	254	170	84
Lymphoma-leukæmia .. .	72	27	45
Others	75	20	55

DISCUSSION

Cancer cells were detected in the serous fluids of 54% of all patients with cancer and effusion. This is not a high figure when compared with some other published results of recent years,^{3 4} but our method of tabulation is unusual because it expresses *decisively* "positive" results which were reported as such. Many workers have augmented their successful detection of cancer by combining positive and suspicious results; and some analyses have been based, at least partly, on retrospective examination of cytological preparations after the final diagnosis has been more or less settled.

Our findings show that the successful detection of cancer cells in serous fluids depends to a great extent on the type of cell composing the neoplasm. For example, cancer cells were detected in 67% of all cases of adenocarcinoma with effusion; the corresponding figure for the lymphoma-leukæmia group is reduced to 38%, and it is only 27% for all the other neoplasms. Presumably, some of these differences are due to the inherent tendency of certain neoplasms not to disseminate their cells as freely as others do. Squamous-cell carcinoma is a good example of this: there were 22 patients with bronchogenic squamous-cell carcinoma and pleural effusion; in not one of the fluids from these cases were cancer cells detected. The detection of cells of sarcomas, exclusive of the lymphoma-leukæmia group, was almost nil. Detection of oat-cell carcinoma was distinctly better, however: fluids from 5 of 8 cases were positive.

To some extent the successful detection of cancer cells also depends on the source of the serous effusion, and the site of the primary neoplasm. Pleural fluids were positive in 60% of the cases of cancer with pleural effusion, and in 47% of the cases with ascites the ascitic fluids were positive. Fluids were more likely to be positive with adenocarcinomas of certain organs than of others: ovary 83%, breast 63%, lung 51%, and gastrointestinal tract 50%.

It was nearly always possible from the examination of exfoliated cancer cells to classify accurately the neoplasm into its histological type, such as adenocarcinoma, oat-cell carcinoma, and so on. But only very occasionally was it possible to suggest with confidence the primary site of a neoplasm, because most of the positive fluids contained adenocarcinoma cells which, no matter where the primary neoplasm originated, shared many similarities with each other.

What is the likelihood of a positive report being incorrect? Obviously, this will vary among different laboratories. We issued 283 positive reports, and of these only 2 were incorrect. The first error arose within a few weeks of starting cytology, and it can be attributed to inexperience; the second, which did not occur until almost six years later, can be best described as a lapse of judgment. In both cases, the mistakes were due to the misinterpretation of hyperplastic or hypertrophic mesothelial cells—a notorious pitfall of cytodiagnosis.

It is more difficult to explain false-negative results. Though now, with more experience, it is obvious that some ought to have been reported as positive, nonetheless most of the false-negative smears are, on review, still

1. Vickers, H. E. *Lancet*, 1962, ii, 139.

2. Hazard, J. B., McCormack, L. J., Belovich, D. *J. Urol.* 1957, 78, 182.

3. Luse, S. H., Reagan, J. W. *Cancer*, 1954, 7, 1167.

4. von Haam, E. *Acta cytol.* 1962, 6, 508.

negative. One reason for them is the previously mentioned comparatively slight dissemination of cancer cells by certain neoplasms. Another reason, especially in the case of lymphocytic lymphomas, is the similarity of the exfoliated neoplastic cells to their benign prototypes, thus making their recognition as cancer cells much more difficult, if not impossible. But most false-negative reports were issued on fluids whose formation was probably caused by either neoplastic obstruction of vascular channels, or inflammation, or both. Such fluids may have never contained cancer cells at all.

The serous fluids of 35 patients were reported as "suspicious"; 5 of these patients had no cancer, and the remaining 30 had. Subsequently, 12 of these 30 patients had positive fluids. A number of the suspicious reports are, on review, distinctly positive, and probably they would not give rise now to any difficulty of diagnosis. The proportion of suspicious reports has diminished over the years, and during the past three years not one such report was issued on a fluid from a patient without cancer.

The clinicians at this medical centre have usually sent at least one specimen of fluid for cytological examination from any patient who had a serous fluid aspirated. Occasionally, the finding of cancer cells exposed an unsuspected cancer, although more commonly, it provided the clinician with the information that a known or suspected cancer had spread incurably. Thus, with the prognosis apparent, the possibility of a surgical operation or radiotherapy being curative was excluded, and any form of treatment became a matter of palliation. A negative cytological report ought not to have eliminated cancer from the differential diagnosis; rather, when the presence of cancer was suspected, it should have compelled the clinician to rely more on other diagnostic procedures.

One of these other diagnostic procedures was needle biopsy of the pleura, though this was clearly demonstrated to be inferior to exfoliative cytology of pleural fluids in the diagnosis of cancer. In 81 cases of cancer the aspiration of pleural fluid was accompanied by needle biopsy of the pleura; the fluids were positive in 39 cases, and the biopsy specimens exhibited definite neoplasm in 19 of the 81 cases. 13 of these 19 cases also had positive fluids; therefore, in only 6 cases was the pleural biopsy specimen positive and the fluid negative, whereas in 26 cases the fluid was positive and the biopsy specimen negative.

The examination of serous fluids was the least time-consuming of cytological examinations because nearly all positive smears contained numerous cancer cells which were recognised after only a brief examination. Usually, only the negative and suspicious smears required complete systematic screening, which can be carried out in a few minutes by an experienced technician. The stained wet-film proved to be extremely useful: it often enabled us to give a negative or positive report on a fluid within about fifteen minutes of receiving a specimen in the laboratory—an advantage for clinicians and patients alike. When a wet-film was positive, we postponed the staining of the permanent smears until just before the stains were due to be discarded, because when smears contained numerous cancer cells some were liable to be dislodged during processing, when they could contaminate smears of other cases. Occasionally the cell-block technique of fixing and sectioning the centrifuged deposit was also used, though rarely did it provide us with information that could not be obtained by examination of smears alone.

The bulk of our cytological work of about 12,000 smears a year was examined by specially trained technicians who were responsible for issuing most of the negative reports, and consequently we had to spend only a small proportion of our time in examining smears. It is the ideal arrangement for the pathologist with other duties, but it requires enough cytological work to justify the employment of cytotechnicians.

Interest, plenty of good material, and much experience are essential for acquiring proficiency in any kind of exfoliative cancer cytology. Probably the most efficient way to begin cytology is to study under an expert. One of us had the good fortune to do this, and he passed on what he had learned to the other. It is fallacious for the pathologist to assume that, because he is widely experienced in morbid anatomy and histopathology, he is also qualified to practise cytology. He must learn once more. In fact, some most outstanding cytologists, including Papanicolaou himself, have not been pathologists. We regard the pathology laboratory as the appropriate environment for exfoliative cytology, however, and the histopathologist, familiar with the many varieties of tissue change, as the person best suited to learn it.

In conclusion, we consider that one thing is certain: exfoliative cytology can be successfully employed with serous fluids, and therefore it ought to be more widely pursued.

SUMMARY

935 serous effusions from 634 patients were examined for cancer cells. Fluids from 217 (54%) of the 401 patients with cancer were decisively "positive".

Cancer cells were most likely to be detected in the effusions of patients with adenocarcinomas, or with neoplasms of the lymphoma-leukæmia group. Cells from other sarcomas or from squamous-cell carcinomas were rarely detected.

Most "false-negative" reports were attributed to the fact that many serous fluids from patients with cancer never contain cancer cells. "Suspicious" reports were not common.

Exfoliative cytology of pleural fluids was shown to be clearly superior to needle biopsy of the pleura in the detection of cancer.

This experience indicates that exfoliative cytology of serous effusions is practicable and useful.

"... I have met also research workers and administrators who think that the way to 'take care of statistics' in a medical school, in which hundreds of investigations are being conducted, is to appoint a solitary statistician. This attitude apparently springs from the belief, which I have heard expressed by some investigators, that a little bit of statistical advice is necessarily better than none at all. This, in my opinion, is by far the most serious problem that meets the 'all-purpose' statistician in a medical school. If a physician, on the basis of insufficient information, makes a wrong diagnosis and, because a prescription is demanded, prescribes something that kills the patient, is that better than not prescribing at all? A statistician is called in, ostensibly at least, to improve the scientific quality of a piece of research. Is it not therefore a subject for Mephistophelian laughter if, owing to insufficient time and inadequate information about the project, the statistician actually reduces its scientific quality? This was the thought that prompted a statistician, who knows what scientific research really entails, to say to me: 'I feel unclean whenever I have had one of those consultations.'"—Prof. DONALD MAINLAND, *Notes from a Laboratory of Medical Statistics*, no. 55, p. 2.