Malignant meningitis: a rational approach to cerebrospinal fluid cytology

J M MacKenzie

Abstract

Aim—To clarify laboratory guidelines for cerebrospinal fluid (CSF) cytology.

Methods—Clinical and pathological data relating to 54 patients with cytologically malignant cells in the CSF were reviewed, together with CSF cell counts and protein measurements for 29 patients. Utilising this data, criteria were established for CSF cytology and validated by review of 100 patients in whom CSF cytology had not been carried out on the basis of these criteria.

Results—There was only one false positive diagnosis of malignancy on the basis of CSF cytology. All patients with malignant cells in the CSF fulfilled at least one of the following criteria: clinically known or suspected malignancy; raised cell count; raised protein concentration. In none of the 100 patients, in whom cytology was not performed, was the diagnosis of malignant meningitis missed.

Conclusion—Cytology should be performed on CSF specimens from all patients with known, or suspected, malignancy, but in other cases, only if the cell count or protein concentration, or both, is raised.

Keywords: malignancy, cerebrospinal fluid, cytology.

Various attempts have been made to establish guidelines for laboratory examination of cerebrospinal fluid (CSF).1 2 Physician microscopy of CSF samples with normal cell counts has been shown to be unnecessary and wasteful of resources.3 Furthermore, if the opening pressure, cell count and protein concentration are all normal, additional procedures are rarely of value.4 CSF cytology is principally useful in the identification of malignant cells, as the cytological changes in inflammatory and other non-neoplastic disorders are non-specific.5 6

The progress of non-neoplastic conditions can be monitored by CSF cell count/differential, protein and glucose concentrations measured by a biomedical scientist without the necessity of the use of expensive pathologist’s time in performing cytology. Suspected infections require proper microbiological investigation of the CSF and identification of organisms in a cytological preparation is probably only an aesthetic reward for the pathologist and contributes little, if anything, to the patient’s management. Yet clinicians frequently adopt the “blunderbuss” approach to requesting of laboratory tests on CSF without due regard to the propriety of tests in the clinical circumstances, with cytology, cell count, protein, glucose, oligoclonal bands, and microbiology often being requested routinely, and pathologists often feel a moral obligation to carry out the tests requested, even if this has no rational basis.

This study sought to clarify criteria by which the pathologist can decide when CSF cytology is likely to contribute to the patient’s management, and minimise the number of unnecessary cytological tests, firstly, by defining under what circumstances malignant cells are likely to be found in the CSF and, secondly, by validating these criteria in practice.

Methods

From 1980 to 1990, cytology was carried out on all CSF specimens received in the Neuro-pathology Laboratory of the Walton Centre for Neurology and Neurosurgery, Liverpool. During that period 5808 cytological specimens were received. All of the reports were reviewed and, in CSF samples from 132 patients, cells variously described as “malignant”, “atypical” or “suspicious” had been described. All of the cytospin preparations from these patients were re-examined and CSF samples from 54 patients contained cells which were regarded as definitely malignant.

The clinical details and histological material (where available) relating to these 54 patients were reviewed in order to (1) confirm that the diagnosis of malignancy on the basis of CSF cytology was correct and (2) identify criteria by which the decision whether or not to perform cytology could be made in the laboratory. To assist in the second objective, cell counts and protein concentrations, available for 29 of the patients, were also utilised.

Having established, and implemented, the criteria 100 cases from 1992 to 1993 for which complete clinical records were available, and in which cytology had not been carried out on the basis of these criteria, were randomly selected and thoroughly reviewed to establish whether there was any possibility that a case of malignant meningitis had been missed.

Results

ACCURACY OF CYTOLOGICAL DIAGNOSIS

Fifty of the 54 patients with malignant cells in the CSF had confirmed malignancy, either known at the time of CSF sampling (43 patients) or subsequently confirmed by clinical, radiological or pathological investigation (seven patients). Of the remainder, three were...
Table 1  Types of malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>25(50%)</td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
</tr>
<tr>
<td>Lung</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>3</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>2</td>
</tr>
<tr>
<td>Uncertain</td>
<td>1</td>
</tr>
<tr>
<td>Primary CNS</td>
<td>11(22%)</td>
</tr>
<tr>
<td>PNET</td>
<td>7</td>
</tr>
<tr>
<td>Glioma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Germinoma</td>
<td>1</td>
</tr>
<tr>
<td>&quot;Pinealoma&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Haemopoietic</td>
<td>10(20%)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>6</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3(6%)</td>
</tr>
<tr>
<td>Seminoma</td>
<td>1(2%)</td>
</tr>
</tbody>
</table>

Table 2  Clinical diagnosis at time of CSF sampling (malignancy subsequently confirmed)

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Number (confirmed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant meningitis</td>
<td>50</td>
</tr>
<tr>
<td>Known primary</td>
<td>43</td>
</tr>
<tr>
<td>Suspected primary</td>
<td>7(4)</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>2(2)</td>
</tr>
<tr>
<td>Benign intracranial hypertension</td>
<td>1(1)</td>
</tr>
<tr>
<td>Headache/arachnoid cyst</td>
<td>1</td>
</tr>
</tbody>
</table>

Malignancy subsequently found to have a malignancy—PNET in two cases and a bronchial carcinoma in one. A fourth, the false positive case, had headache and an arachnoid cyst.

**Malignancy**

were primitive
Melanoma
3(6%)
OF
Malignancy
were
primitive
Melanoma
3(6%)
OF
Malignancy
were
leukaemia
adenocarcinomas
whom

tuberculous
malignancy
have
suspected
of
malignancy
at
the
time
of
CSF
sampling.
All
of
the
patients
not
suspected
of
having
malignancy
at
the
time
of
sampling
had
a
raised
cell
count
or
protein
concentration,
or
both.

Therefore,
all
of
the
cases
with
malignant
cells
in
the
CSF
fulfilled
at
least
one
of
the
following
criteria:
clinically
known
or
suspected
malignancy;
raised
cell
count;
raised
protein
concentration.
In
practice,
most
had
all
three.

**REVIEW OF CASES IN WHICH CYTOLOGY WAS NOT CARRIED OUT**

Of
the
100
cases
reviewed
in
which
cytology
had
not
been
carried
out
on
the
basis
of
these
criteria,
only
two
had
malignancy
at
the
time
of
CSF
sampling
(carcinoma
of
the
head
of
the
pancreas;
multiple
myeloma)
and
one
subsequently
developed
it
carcinoma
of
breast
two
years
later).
There
was
no
evidence
in
any
of
these
cases
that
the
malignancy
involved
the
CSF
pathways
at
any
time
or
that
malignant
cells
could
have
been
present
in
the
CSF
and
missed
by
not
carrying
out
CSF
cytology.

**Discussion**

In
only
one
of
the
54
patients
whose
CSF
contained
cytologically
malignant
cells
does
the
diagnosis
seem
to
have
been
wrong.
It
is
highly
unlikely
that
a
patient
with
carcinomatous
malignancy
would
be
symptom-free
and
well
26
months
after
his
initial
presentation.

Although
50
patients
with
CSF
malignant
cells
were
thought
clinically
to
have
malignant
malignancy
at
the
time
of
CSF
sampling,
43
of
whom
already
had
a
known
primary
malignancy,
there
was
a
small,
but
highly
important,
group
of
patients
in
whom
the
diagnosis
was
not
suspected.
Two
of
these
were
thought
to
tube
malignancy
and
one,
bien
intracranial
hypertension.
One
of
the
former
subsequently
developed
a
bronchial
carcinoma
and
the
others,
PNETs.

Any
system
of
selection
of
CSF
for
cytology
in
the
laboratory
must
ensure
that,
whilst
mini-
malignant meningitis, in whom the diagnosis is not suspected clinically, are not missed. The malignant meningitis, missing unnecessary procedures, patients with malignant meningitis, in whom the diagnosis is not suspected clinically, are not missed. The CSF cell count and protein are useful screening procedures in this respect. In the present study, only one patient had a normal cell count and protein concentration and she was strongly suspected, on clinical and radiological grounds, of having malignancy involving the CNS. None of the patients in whom the diagnosis of malignancy was not suspected clinically had a normal cell count and protein concentration. In other words, all patients with malignant cells in the CSF fulfilled at least one of the following criteria: clinically known or suspected malignancy; raised CSF cell count; raised CSF protein concentration; and, in practice, most fulfilled all three. This is in accord with the results of Hayward et al who found that all of their 52 patients with malignant meningitis had at least a raised cell count or protein concentration or opening CSF pressure. CSF cytology is mandatory in all cases of known, or strongly suspected, malignancy. This is particularly true in cases of leukaemia and lymphoma, where the results of CSF cell counts and cytology are important factors in determining and monitoring treatment. However, selection of cases without known or suspected malignancy may be undertaken on the basis of CSF cell count and protein; if both are normal, then malignant cells are almost certainly not present and cytology is unnecessary, a conclusion corroborated by the fact that no cases of malignant meningitis were identified in the 100 cases reviewed in the present study.

It is acknowledged that although such a policy reduces the number of unnecessary CSF cytological examinations, some of the examinations undertaken on CSF from patients not thought to have malignancy will still be valueless. Further selection of samples for cytology can be made on the basis of clinical information—for example, cytology is unnecessary, even if the cell count and protein concentration are raised, if the patient has recently undergone an invasive neurological procedure for a non-neoplastic lesion or if there is a clear clinical history of multiple sclerosis or subarachnoid haemorrhage.

It should be possible to select cases for CSF cytology on the basis of cell count and protein concentration, where cytopathology or neuropathology departments are closely related to chemical pathology and microbiology departments, or where information technology is shared. In light of the increasing drive towards "market testing" of pathology services, reducing unnecessary CSF cytology is one way in which cytopathology and neuropathology providers can reduce their costs.

In conclusion, this study has provided some criteria by which the laboratory may decide when CSF cytology is likely to be of value, and so minimise the number of profitless CSF cytological examinations, whilst ensuring that patients with suspected or unsuspected malignant meningitis are correctly diagnosed and managed.

Addendum
Since completion of this study, another patient was encountered in whom the diagnosis of malignant meningitis was not suspected clinically. Cytokeratin and epithelial membrane antigen positive malignant cells were identified in the CSF on two separate occasions, despite a clinical diagnosis of benign intracranial hypertension. However, the CSF protein concentration and cell count were both raised at 0.82 g/l and 156 white cells/mm³, respectively.

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