TUMOR CELLS IN THE CEREBROSPINAL FLUID*

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The armamentarium of the neurosurgeon in the diagnosis of intracranial neoplasm has increased considerably in the past 4 decades. However, the considerable number of “negative” surgical explorations and intracranial neoplasms actually missed indicate that new techniques are still needed.

During the last 7 years we have become interested in the examination of the sediment of the spinal fluid as an aid in the diagnosis of intracranial tumors. It seemed clear that cytologic examination of the cerebrospinal fluid for tumor cells might play a significant role in the recognition of these neoplasms. While most of the reported studies described cells from metastatic brain lesions, only a few investigations demonstrated tumor cells derived from primary intracranial tumors in the spinal fluid.

We propose to present a short review of the pertinent literature followed by a detailed description of 3 cases in which the cytologic findings in the spinal fluid aided in the diagnosis of intracranial tumor. Subsequently, the over-all result of a study on 2,270 cases in which the patient was suspected of having a neoplasm of the central nervous system is mentioned briefly.

At Michael Reese Hospital all specimens of spinal fluid from the neurosurgical and neurological services are sent routinely for cytologic examination. The fluid, usually 3 to 6 cc., is centrifuged rapidly for 5 min. The sediment, which frequently is only microscopic in amount, then is smeared at once on two albumin-coated slides and immersed immediately in a solution of 95 per cent alcohol. The slides are stained according to Papanicolaou’s method. In addition, all ventricular fluid obtained from ventriculography is sent for cytologic diagnosis. This specimen is prepared in the same manner as the cerebrospinal fluid from spinal puncture. The cells present in the ventricular fluid are interpreted in the same manner as those in the fluid obtained by spinal puncture. It is clear that there will be many more and better preserved tumor cells in the ventricular fluid if the tumor has extended into the ventricles.

Platt, citing a number of older studies, remarked that cytologic examination of spinal fluid does not supplant other neurologic procedures in the diagnosis and localization of tumors of the central nervous system, but should be used in combination with other existing methods. He reported 8 cases in which cytologic examination of the spinal fluid disclosed atypical cells. The sediment in the spinal fluid of 1 patient with glioblastoma multiforme showed atypical pleomorphic nuclei and of another, sheets of malignant tumor cells. The spinal fluid of a patient with medulloblastoma revealed cells with hyperchromatic nuclei and numerous mitoses. Atypical cells with hyperchromatic nuclei were found in an instance of sarcomatosis of the meninges. Hyperchromatic cells with pyknotic nuclei (Class IV-V of Papanicolaou’s classification) were derived from a Rathke’s pouch cyst. Cells suggestive of malignant tumors were present in cases of glioblastoma multiforme, astrocytoma and oligodendroglioma.

McCormack et al., in 1953, demonstrated carcinoma cells in the spinal fluid in 9 of 40

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patients with metastatic carcinoma. Larson et al. reported tumor cells in 5 instances: 3 metastatic carcinomas and 2 gliomas. Spriggs found carcinoma cells in the spinal fluid in a high proportion of his cases. He also reported positive findings in patients with a glioblastoma multiforme, a medulloblastoma, a reticulum-cell sarcoma and a myeloma, respectively.

Murphy stressed clumping of tumor cells in the spinal-fluid sediment in instances of carcinomatosis of the meninges. McCormack et al., in 1957, found neoplastic cells in the spinal-fluid sediment in 27 out of 320 patients. The majority of these patients had metastatic carcinoma. McMenemey and Cumings, described 13 cases in which there were tumor cells in the spinal fluid. There were 8 metastatic carcinomas and 5 primary tumors—an astrocytoma, a menigioma, an oligodendroglioma, a chromophobe adenoma, and a chordoma. Marks and Marrack reported 7 instances of metastatic carcinoma with positive findings in the spinal fluid.

From these reports it is evident that carcinoma cells from metastatic brain lesions are detected much more commonly than cells from other tumors.

CASE REPORTS

Case 1. A 59-year-old white male was admitted to Michael Reese Hospital because of intermittent nonprojectile vomiting of 3 months' duration, lethargy, and generalized weakness. Eighteen months previously he had fallen down a flight of stairs and dislocated his shoulder; there was no loss of consciousness. A radiologic diagnosis of peptic ulcer of the lesser curvature of the stomach was made 3 months prior to admission.

Examination revealed bilateral papilledema with unequal pupils, the left being large and reacting slowly to light, while the right one was pinpoint. The cranial nerves were normal except for a right central facial weakness. Abdominal reflexes were present but cremasteric and deep tendon reflexes were absent. Bilateral Gordon and Oppenheim reflexes were present. There was general weakness of muscles in all extremities. Vibratory and pain sensations were intact.

Lumbar puncture revealed an opening pressure of 600 mm. of water, the fluid being clear and colorless. Cytologic examination of the cerebrospinal fluid disclosed 1–2 lymphocytes per high power field. In addition, scattered over the slides were occasional, large, single cells, approximately 20 micra in diameter. The nuclei were enlarged, hyperchromatic and somewhat irregular in shape. Often there was only a rim of cytoplasm (Fig. 1).

The laboratory data were normal except for a hemoglobin of 10.8 gm. Films of the skull showed no cranial or intracranial abnormality. The roentgen-ray findings of the gastrointestinal tract revealed a gastric ulcer in a lesser curvature, penetrating into the pancreas.

On the 3rd hospital day ventriculography was performed via parietal burr holes. The ventriculogram showed no localizing evidence of tumor. A right subtemporal decompression was then performed.

Cytologic examination of the ventricular fluid obtained at operation revealed isolated malignant tumor cells of the same type as were seen in the cerebrospinal fluid. However, the cells were somewhat better preserved and more numerous (Fig. 2). These cells were interpreted as metastatic carcinoma cells. The patient's condition deteriorated progressively. Based on the cytologic findings, a diagnosis of gastric malignancy with
cerebral metastasis was made. Thirteen days after operation the patient expired.

Autopsy revealed a primary gastric adenocarcinoma with metastases to regional lymph nodes. The leptomeninges and portions of the cerebral cortex had been invaded by metastatic carcinoma (Fig. 3).

Case 2. A 50-year-old white female was first admitted to Michael Reese Hospital because of an episode of syncope. She had fainted and remained unconscious for approximately 15 min. Upon regaining consciousness, she was aphasic for about 2 min., but regained normal speech shortly thereafter. There were no residual and no premonitory symptoms.

Examination disclosed an arterial blood pressure of 120/70. There were no neurological or skeletonmuscular abnormalities except for a slight blurring of the left optic disc. Hemogram and urinary findings were normal.

Lumbar puncture yielded clear and colorless fluid under pressure of 150 mm. water; protein was 20 mg. per cent. The cerebrospinal fluid contained many polymorphonuclear leukocytes, 3-4 lymphocytes per high power field and a few meningeal cells. There were occasional loose clusters of elongated, slightly irregular nuclei with a small amount of an eosinophilic cytoplasm (Fig. 4). These cells were interpreted as tumor cells, most likely those of an astrocytoma.

The electroencephalogram was normal with waking pattern of 8-9 sec. rhythm of normal voltage. Roentgenograms of the skull were interpreted as showing no abnormalities. The patient was discharged without having any further neurological symptoms, only to be readmitted 5 months later.

For 6 weeks she had been somewhat confused, and frequently could not recall recent events or pronounce familiar names. Since the preceding month she had become extremely euphoric and had lost 10 pounds.

On examination she showed slight mental confusion. An electroencephalogram revealed irregular slow waves of moderate voltage in the left frontal and temporal leads. A carotid arteriogram showed a mass in the left frontobasal area, with anterior displacement of the anterior cerebral artery and superoposterior displacement of the middle cerebral artery.

Ventriculography indicated a displacement of the left lateral ventricle. By means of a ventricular cannula 15 cc. of yellow fluid were obtained.

The ventricular fluid contained numerous polymorphonuclear leukocytes and red blood cells. Elongated cells, about 10-12 micra in size, as well as rounded hyperchromatic cells with little cytoplasm and prominent nucleoli were present in moderate numbers (Fig. 5). Upon removal of the cannula, gray-white gelatinous material oozed from the tract. Microscopic preparations of this cerebral tissue revealed an astrocytoma Grade III-IV (Fig. 6).

The patient made an uneventful postoperative recovery but there was no improvement in symptoms.

Case 3. A 5-year-old boy was admitted to Michael Reese Hospital because of increasingly
severe headaches of 1 month's duration, occurring in the frontal and bitemporal areas with some radiation to the upper part of the back. For 2 weeks he had been nauseated with frequent vomiting, usually in the morning upon arising. One week before admission bilateral internal strabismus developed with resultant diplopia and his gait was unsteady.

Examination disclosed an alert child with unsteady gait. The pupils were equal and reacted well to light and in accommodation. Diplopia and nystagmus on left lateral gaze were present. There was 3+ papilledema of both optic discs. There was moderate weakness of the right side. The deep tendon reflexes were brisk bilaterally, nuchal rigidity was not present, and the Romberg test was negative.

Hemogram and urinary findings were normal. Roentgenogram of the chest was normal. An electroencephalogram showed irregular slow-wave activity in both frontal areas, but particularly in the right occipital area. There was no seizure activity.

On the 3rd hospital day ventriculography was performed. This showed dilatation of the entire ventricular system with displacement of the aqueduct and the 3rd and 4th ventricles to the right. During ventriculography, 60 cc. of cerebrospinal fluid were removed. Cytologic preparations showed small, round cells, about 10-15 micra in size, with irregular, hyperchromatic nuclei and scant cytoplasm (Fig. 7). These were interpreted as tumor cells. Because of their size and round shape, they were thought to derive from a medulloblastoma.

A suboccipital craniotomy was then performed which revealed a mid-line tumor of the 4th ven-
tricle which extended posteriorly through the mid-
plane of the cerebellar tonsils. The tumor ap-
peared grayish-pink. Not all of it could be re-
moved. There was some herniation of the cerebel-
lar tonsils through the foramen magnum.

Microscopic sections of the operative specimen
revealed round cells with pleomorphic nuclei
with mitoses and scant cytoplasm. Some areas
were arranged in pseudo-rosettes (Fig. 8). This
was consistent with a medulloblastoma.

The patient was discharged on the 19th hos-
ital day to have a 4-week course of radiation
therapy (3500 r.u.) to the cerebrospinal axis.

At this time, 5 years later, the child is still living
and well.

DISCUSSION

In all these 3 cases tumor cells were found
in the cerebrospinal and/or ventricular fluid.
As stated above, most cases on record involve
the demonstration of carcinoma cells in the
spinal-fluid sediment. It is obvious that some
carcinoma cells are not difficult to detect.
Large bizarre cells were found in Case 1. The
cells differed markedly from inflammatory
cells or ependymal cells. Because metas-
tases often involve the meninges, these neo-
plastic cells frequently are exfoliated into
the cerebrospinal fluid and hence can be seen
by the cytologist.

Two patients had primary tumors of the
cerebrospinal system. The findings of tumor
cells in such instances are recorded much
more rarely. In Spriggs' studies the cells
shed from a glioblastoma multiforme were

12-22 micra with usually single nuclei con-
taining finely scattered chromatin. Larson
et al.² described cells of two astrocytomas as
spindle-shaped glia cells. Naylor§ found cells
characteristic of astrocytoma in material
aspirated from intracranial cysts and the
ventricular fluid. The cells showed irregular
hyperchromatic nuclei with relatively large
nuclei. In 1 case of astrocytoma McMen-
emy and Cumings² described tumor cells
resembling epithelial cells.

In our Case 2, an astrocytoma (Grade III)
had involved the meninges. The character-
istic cells were elongated and not related to
inflammatory or meningeal cells. The cells
were enlarged with irregular nuclei and scant
cytoplasm. From our experience, meningeal
cells which normally may be present in the
sediment are usually flattened, rather regular
in shape, and sometimes intermingled with
inflammatory cells.

In our Case 3, the cells shed from a med-
ulloblastoma were clustered and had small
round and hyperchromatic nuclei and scant
cytoplasm. In Walt's case the cells were
large, usually single, but appeared occa-
sionally in clumps with eccentrically situated
nuclei and a moderate amount of cytoplasm.
Platt,∞ in his study of fluid aspirated from

Fig. 7. Case 3. Cells from ventricular fluid of patient
with medulloblastoma. Note the cluster of small,
rounded, hyperchromatic cells with scant cytoplasm.
Papanicolaou preparation, X785.

Fig. 8. Case 3. Medulloblastoma. Note the small
cells arranged in clusters. Hematoxylin and eosin
preparation, X430.
the cisterna magna, actually described pseudo-rosettes composed of large vesicular and hyperchromatic nuclei. Spriggs described cells ranging in size from 9–15 micra. They often were arranged in clumps and showed practically no recognizable cytoplasm. It is well known that medulloblastomas frequently invade the meninges and that they are composed of loosely arranged cells which apparently exfoliate easily.

These 3 instances of intracranial tumors in which malignant cells were discovered in the cerebrospinal fluid illustrate the fact that tumor cells may be found in the cerebrospinal fluid and/or in the ventricular fluid if tumor is present in the meninges or has extended into the ventricles or subarachnoid space. It is essential to differentiate tumor cells from cells normally appearing in the cerebrospinal fluid. Such non-neoplastic cells include inflammatory cells, ependymal cells, meningeal cells, histiocytes and sometimes squamous cells. It has been our experience that every cell that cannot be identified as one of the above should be regarded as suspicious of tumor.

During the past 5 years we have studied the spinal-fluid sediment of 2,270 patients suspected of having neoplasms of the central nervous system. Of these, 110 later were found to have surgical or autopsy evidence of tumor. In 44 of these 110 instances, a study of the sediment of the cerebrospinal fluid disclosed tumor cells (40 per cent of the cases). While at the first glance this may be a very low percentage of positives, it should be pointed out that a positive cytologic finding may be the only evidence that the patient has an intracranial tumor at a time when all other tests are negative or inconclusive.

It is important to remember, as Larson et al. stated, that “any tumor capable of exfoliation can lead to the finding of tumor cells in the spinal fluid if either the ependyma of the ventricles or the leptomeninges are involved.”

**SUMMARY**

The finding of malignant cells in the cerebrospinal fluid stained according to the Papanicolaou method is discussed. Three cases of neoplasm of the central nervous system with positive cells in the spinal fluid are presented: 1 case of metastatic carcinoma, 1 case of astrocytoma, and 1 case of medulloblastoma. The cytologic findings are emphasized and the factors leading to exfoliation of cells are presented. The results of studies of 110 instances of cerebrospinal tumors are reported briefly.

**REFERENCES**