INTRACRANIAL METASTASIS AS EARLIEST EVIDENCE OF CARCINOMA OF THE LUNG

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During the past four years it has been my experience in two cases to disclose metastatic carcinomatous lesions of the brain unexpectedly at operation. At autopsy later on these were shown to have originated from primary bronchogenic carcinoma of the lung. In both cases the final preoperative diagnosis was primary brain tumor. Although a metastatic lesion of the brain was suspected in Case I, no primary tumor could be revealed by a most exhaustive clinical investigation; in fact, the primary site of the tumor in this case was not revealed until autopsy, one year and ten months after the intracranial operation. In the second case, the presence of a metastatic lesion of the brain was not suspected until the ventricular cannula encountered unusual brownish mucoid material deep in the brain substance during the operation of ventriculography. Chiefly because of the diagnostic problems presented by these cases, it has been considered worth while to report and discuss them in some detail. Surgical therapy in such cases will also be discussed briefly.

Case 1: A white woman, aged 49 years, was referred to the Clinic on January 11, 1932, by Dr. J. S. Zimmerman of Youngstown, Ohio. Her chief complaints were "pains in the head" and vomiting. She had been in good health until the summer of 1931, when she began to have suboccipital headaches which lasted for an hour or two and recurred about once a week. The headaches became more frequent and more severe, and in November, 1931, they were accompanied by nausea, vomiting, and blurring of vision. After November, 1931, suboccipital headaches occurred in bouts lasting only a few minutes and subsiding rapidly. These bouts recurred as often as ten times daily and were usually accompanied by vomiting. At such times there were occasional, momentary lapses of consciousness, but no prolonged coma. The attacks were described as "sudden blinding attacks of headache." No convulsions, paralysis, dizziness, deafness, or staggering occurred, and there had been no cough, dyspnea, hemoptysis, or pain in the chest.

General physical examination revealed a weak, anemic woman with sallow, dry skin. The pulse rate was 100 and the blood pressure was 116 systolic, 66 diastolic. There was no evidence of cardiac, pulmonary, or intra-abdominal disease. Pelvic and rectal examinations revealed no abnormalities.

Neurological examination was entirely negative except for diminished corneal reflexes in both eyes. Vision 6/30 O.D.; 6/30 plus 1 O.S.

Ophthalmoscopic examination revealed definite edema of both discs, 1.5 diopters O.D. and 2.5 diopters O.S. There were some hemorrhages in the left retina and the vessels were tortuous. Examination of the visual fields showed enlargement of both blind spots. The patient did not coöperate well during this examination.

Otolaryngological examination showed no abnormality in the nose, throat, larynx, or ears.

Laboratory work: The skull was reported to be normal by roentgen examination. Lumbar puncture obtained clear, colorless, cerebrospinal fluid under normal pressure and there was no block as shown by the Queckenstedt test. Examination of the fluid showed three cells, faint trace of globulin, 50 mg. total protein, negative Wassermann and Kahn reactions, colloidal gold curve 2-2-2-1-1-1-0-0-0-0. Urinalysis showed no abnormalities and the blood Wassermann reaction was negative. Examination of the blood showed 3,780,000 red cells, 9,650 white cells, and 71 per cent hemoglobin.

After completion of the above examinations, a tentative diagnosis of unlocalized brain tumor was made. Because of the fact that the general appearance of this patient suggested that a cryptic malignancy might be present elsewhere in the body, it was considered advisable to carry out the following examinations in an effort to locate a primary tumor from which an intracranial metastasis might have arisen:

Roentgen examination of the chest showed no evidence of pulmonary neoplasm or abscess.

Roentgen examination of the gallbladder and of the entire gastro-intestinal tract showed no abnormality.

Gastric analysis showed no free hydrochloric acid.

On January 18, 1932, in an effort to localize the brain lesion, ventriculography was carried out. This revealed a moderate, symmetrical dilatation of both lateral ventricles and of the third ventricle, suggesting a subtentorial lesion.

Operation was performed on January 19, 1932. Cerebellar exploration revealed marked herniation of the cerebellar tonsils through the foramen magnum. On the posterolateral surface of the left cerebellar hemisphere, there was a firm, greyish red area of tumor tissue which was adherent to the overlying arachnoid and dura. There was no evidence of tumor in the fourth ventricle or in the right cerebellar hemisphere. Using the electrosurgical cutting loop, the tumor in the left hemisphere was removed piecemeal. As this procedure continued, the reddish tumor could be traced into the interior of the cerebellum. In some places it appeared to infiltrate the cerebellar substance slightly and in other places it was possible to find a plane of cleavage between pathological and normal tissue. A mass of tissue about the size of a lime was then removed until the walls of the cavity showed the appearance of normal cerebellar tissue. Following this procedure, fluid flowed freely from the fourth ventricle, which previously had been obstructed by the pressure of the tumor in the left cerebellar hemisphere. The wound was closed, leaving the usual adequate decompression of the posterior fossa of the skull.

The patient's postoperative course was smooth and uneventful, and she was discharged from the hospital on the twenty-first day after operation. At that time she was free from headache and was able to use all extremities without ataxia.

Pathological Report (Dr. Allen Graham): Microscopical examination of section of tumor mass from cerebellum shows masses of edematous, hemorrhagic, cerebellar tissue, with large quantities of foam-cells in some areas. There is a tumor mass consisting of alveolar and pseudoglandular structures. The periphery of these consists of a sharply outlined layer of elongated, columnar

cells, with relatively small, round, deeply staining nuclei, separated at the base and resting on a sharply defined stroma. The opposite end of the cell is finely granular and seems to have vacuoles. In some areas, these cells, in single layers, form spaces suggestive of glandular structure. In other areas, the space is filled by a solid mass of these cells, which are of polygonal shape, have considerable pink-staining, reticulated cytoplasm, with many vacuoles, and round or oval, deeply staining, richly chromatic nuclei. The tumor cells seem to be secreting a mucoid material. *Diagnosis:* Tumor of cerebellum, probably metastatic.

Subsequent Course: Two months later the patient was free from headaches, her vision had improved, and she was gaining strength. Examination showed no neurological abnormalities. There was no ataxia or nystagmus, and there was complete recession of papilledema. The patient's progress was favorable for nine months, during which time she was free from headaches and vomiting, although she failed to gain weight and continued to appear thin and emaciated. Then she began to lose ground and had occasional headaches, vomiting, and mental confusion. In October, 1932, examination of the eyes showed a choked disc of one diopter in each eye, and lumbar puncture showed clear, colorless fluid under increased pressure (240 mm.). The spinal fluid contained five cells, a marked trace of globulin, and 48 mg. total protein. It was evident that the intracranial pressure was moderately increased, perhaps due to recurrence of the tumor. Another operation, however, was not considered advisable at that time.

At home the patient declined from October, 1932, to January, 1933, and she was in a semi-stuporous condition much of the time. From January to July, 1933, temporary improvement was noted; there was no headache or vomiting, and although the patient was mentally clouded, she was able to stand on her feet, ask for food, recognize friends, and go for automobile rides. After July, 1933, she was confined to her bed until the time of her death, November 18, 1933. During this final period, she could not feed herself, her consciousness was greatly clouded, she became weak and lost weight, and weakness of the left arm and contracture of the left leg developed. On November 5, 1933—two weeks before death—she was observed at her home, where she lay in bed, greatly emaciated, with spastic paralysis of the left arm and left leg, and unable to eat or speak. She appeared to be awake and conscious, but lay motionless in bed, having the appearance of a cadaver in whom cardiac contractions seemed to be the only objective evidence of life. Obviously, the patient was dying from extensive recurrence of the intracranial tumor. Death occurred quietly November 18, 1933, twenty-two months after operation.

Autopsy, November 19, 1933: In the upper lobe of the left lung, contiguous with a bronchus, there was a firm tumor, which measured 2 x 1.2 cm. in diameter. A second small nodule was found on the external anterior surface of the left upper lobe. Microscopic examination showed a bronchogenic carcinoma. The peribronchial lymph nodes on the left side were also involved. Examination of the brain revealed a large metastatic tumor 6 cm. in diameter on the inferior surface of the right frontal lobe which caused marked compression and distortion of both frontal lobes. The tumor did not invade the left hemisphere. In the right hemisphere the tumor was partially degenerated and cystic, containing thick, mucinous material. There was a small cortical tumor nodule, 8 mm. in diameter, on the inferior surface of the right temporal lobe. Grossly, the

cerebellum showed no recognizable tumor tissue. Sections from the tumor masses in the right frontal lobe, right temporal lobe, and fragments of tissue from the left cerebellar hemisphere showed an adenocarcinoma, similar in all respects to the lesion in the lung and to the tumor which had been removed surgically from the cerebellum twenty-two months before. Therefore, it was our opinion that the original tumor of the cerebellum, as well as the later intracranial recurrences, were all metastatic from the small bronchogenic carcinoma of the left lung.

Discussion of Case 1: The outstanding features of this case are (1) the diagnostic difficulty, (2) the prolonged survival of the patient, and (3) the large size of the intracranial metastases in comparison with the small primary lung tumor.

Although a primary neoplasm in another location was suspected, the lung tumor in this case caused no symptoms or signs, and it was apparently too small to produce a shadow in the roentgen film. Here cerebral metastasis gave rise to the earliest symptoms of the disease.

The survival of this patient for twenty-two months after operation for carcinomatous metastasis to the brain seemed quite surprising to the writer, although Cushing[1] called attention to long postoperative survival periods (five and one-half years, three years, and two years) in such cases. Although this patient was neither a useful nor companionable citizen during the last half of her postoperative course, at least she was free from severe head pain and vomiting.

Case 2: A white man, aged 48 years, was referred to the Clinic February 2, 1936, by Dr. John D. O'Brien of Canton, Ohio. A diagnosis of intracranial tumor had been made. The patient apparently had been in good health until November, 1935, when severe frontal headaches developed which were thought to be due to "frontal sinusitis" or "neuralgia." The headaches gradually became more severe, occurring at times in the temporal and occipital regions, and they were occasionally accompanied by nausea. In December, 1935, failing vision and dizziness were first noticed, and the patient's glasses were changed without relief of headaches. The symptoms became steadily more severe, and the gait became unsteady. He had been in bed for three weeks prior to admittance at the Clinic. He had noticed occasional numbness of the right leg and at times he had difficulty in finding the desired words for vocal expression. There had been no convulsions, paralysis, cough, dyspnea, hemoptysis, or pain in the chest.

General physical examination revealed a somewhat emaciated adult white man who was apparently well oriented and coöperative. The pulse rate was 82 and the blood pressure was 150 systolic, 100 diastolic. There were no signs of pulmonary, cardiac, or intra-abdominal disease. The prostate was normal in size and consistency.

Neurological examination showed sixth nerve palsy of the right eye, sluggish tendon reflexes throughout, absent patellar reflexes, unsteady gait, positive Romberg sign, and transient aphasia.

Ophthalmoscopic examination showed bilateral choked disc, 6 diopters, O.D.; 5 diopters O.S.

Examination of the visual fields could not be made because of inability of the patient to coöperate.

Laboratory work: Urinalysis revealed no abnormalities. Examination of the blood showed 5,280,000 red cells, 9,100 white cells, and 81 per cent hemoglobin. The blood Wassermann test gave a negative reaction. Examination of the cerebrospinal fluid which was obtained from the right lateral ventricle at operation later showed no cells, no globulin, 20 mg. total protein, negative Wassermann reaction, and negative colloidal gold test. Roentgen examination of the skull showed marked demineralization of the clinoid processes.

A preoperative diagnosis of probable cerebellar tumor was made and it was planned to do ventriculography followed by intracranial exploration as indicated by the roentgen findings.

Operation was performed January 5, 1936. The posterior horn of the right lateral ventricle was tapped through the usual drill hole and 25 or 30 cc. of clear, colorless cerebrospinal fluid was obtained under pressure. On attempting to insert a cannula into the posterior horn of the left lateral ventricle, a cystic cavity was encountered at a depth of 5.5 cm. in the left occipital lobe, and thick, brownish, syrupy, mucinous material escaped from the end of the cannula. This fluid was darker and more viscous than that usually seen in gliomatous cysts. Because of the peculiar character of the fluid, it was thought that there might be a metastatic lesion in the left occipital lobe. Air was injected into the right lateral ventricle and roentgen films were made. These showed a marked shift of the ventricular system from the left to the right side of the head. The right lateral ventricle and the anterior horn of the left lateral ventricle were considerably dilated. The posterior horn of the left lateral ventricle was obliterated. It was evident that there was a large space-filling lesion in the left occipital lobe.

Because it was thought that there might be a metastatic lesion from a lung tumor, a single flat roentgen film of the chest was made while the patient was under avertin anesthesia. This film failed to show evidence of a lung tumor.

A left occipital craniotomy was then done, and after revealing the presence of a large subcortical tumor, the whole left occipital lobe was amputated with the electrosurgical unit. Two hours after operation, the wound was reopened in order to deal with intracranial hemorrhage, but in spite of control of bleeding from the dural veins, artificial respiration, and various stimulants, the patient expired during closure of the wound.

Autopsy revealed a small carcinoma of the left main bronchus and a larger tumor nodule, 2.5 cm. in diameter, in the apex of the left lung, with metastasis to the bronchial lymph nodes. There was a cystic metastatic nodule, 3 x 2.5 cm., in the cerebellum, but no more nodules in the cerebrum. The cystic cavity contained brown, mucinous material. Microscopic examination revealed the same histological picture of bronchogenic adenocarcinoma in the surgical and postmortem sections.

Discussion of Case 2: In this case the preoperative diagnosis was probable cerebellar tumor, primary in the cerebellum. The possibility of a metastatic tumor of the brain arising from a primary tumor elsewhere had been entirely overlooked because of the complete absence of symptoms and signs of such a primary growth. There was nothing in the history or in the physical examination to suggest the presence of a primary lung tumor. Such a lesion was not even considered until the ventricular cannula encountered thick, brown, mucinous material in the left occipital lobe; after this finding, a belated and not entirely satisfactory roentgen film of the chest failed to reveal evidence of the lung tumor.

The massive obliteration of the posterior horn of the left lateral ventricle as revealed by the ventriculograms overshadowed in diagnostic importance the general dilatation of the remainder of the left ventricle and the right ventricle and indicated the advisability of operation in the left occipital lobe. Armed with the knowledge of a cerebellar metastasis found at autopsy, it can be said in retrospect that the general dilatation of the ventricles was unquestionably due to obstruction to the outflow of fluid from the fourth ventricle. In the future, ventriculographic evidence and clinical data similar to those found in Case II should suggest the likelihood of multiple lesions of the brain.

General Discussion

In both cases reported, the primary lung tumor was "silent," subjectively and objectively, and even roentgenographically. Symptoms and signs of intracranial tumor were preëminent. Bailey[2] wrote, "Primary bronchogenic carcinoma of the lung so commonly metastasizes to the brain and does it so often before the primary tumor has given symptoms, that it should always be looked for in any patient of middle age, or beyond, who develops rather rapidly symptoms of an infiltrating tumor of the brain." He advised roentgen examination of the chest whether or not pulmonary symptoms were present. Grant[3] reported a case of cerebral metastasis from a lung cancer, which was entirely unsuspected until histological examination of the brain tumor which had been removed at operation revealed the nature of the lesion. Then roentgen examination of the chest was made and this showed evidence of a large lung tumor. Grant stated that the most common primary foci for carcinomatous metastasis to the brain were the breast and lungs. Meagher and Eisenhardt[4], in studying forty-four metastatic intracranial carcinomas in Cushing's series, found that 35 per cent of these lesions originated in primary lung tumors while 25 per cent originated in breast cancers. Fried and Buckley[5] reviewed thirty-eight cases of proved

primary carcinomas of the lung, and found surgical or postmortem evidence of intracranial metastasis in fifteen cases. In the other twenty-three, either there were no metastases to the brain or the brain was not examined. These authors stressed the insidious course of the disease and the frequent occurrence of symptoms and signs of brain metastases as the earliest evidence of primary lung tumor. In eleven of their fifteen cases, the clinical diagnosis was primary tumor of the brain, and lung tumor was overlooked. Rogers[6] found in fifty cases of primary cancer of the lung that the initial symptoms were cerebral in 14 per cent of cases, and he called attention to the high incidence of intracranial metastases from such neoplasms. Elkington[7], in a study of seventeen cases of metastatic tumors of the brain, found that these tumors were secondary to primary carcinoma of the bronchus in nine cases (52.9 per cent). He recommended roentgen examination of the chest in all cases of cerebral tumor of recent onset in elderly people and in all cases of obscure brain disorders suggesting multiple lesions.

From a diagnostic standpoint, then, it is important to bear in mind the possibility of a primary lung tumor in all cases of brain tumor, particularly in patients over 40 years of age. Even in the absence of positive physical and positive roentgen signs, the presence of a primary lung tumor cannot be excluded, because it may be so small or so peculiarly situated as to produce no shadow roentgenographically.

Surgical Therapy

Patients harboring intracranial malignant metastases often suffer from severe headache. Postoperative survival periods have been surprisingly long in some cases. Oldberg[8] reported a postoperative survival period of more than two years in two cases and eight months in another case and gave excellent reasons for suggesting operation on suspected malignant metastases to the brain. Elkington[7] recommended decompression for the relief of headache in such cases.

Cushing[9] stated that operations in such cases "may not infrequently afford a vast degree of symptomatic relief for which patients and their relatives are most grateful. Hence when the unfortunate victims of these disorders once come to be admitted to the hospital wards, it is difficult to refuse their appeals to give them at least the chance of temporary palliation of symptoms which a decompression may afford."

The writer can only agree heartily with the surgical judgment so expressed. Operation should not be performed, of course, when the patient is in poor general physical condition. In addition to decom-

pression as a palliative measure for relief of pain, occasionally, as pointed out by Oldberg[8], it may be possible to remove a single metastatic lesion with prolongation of the patient's life expectancy.

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