METASTASIS TO THE CENTRAL NERVOUS SYSTEM FROM CARCINOMA OF THE LUNG

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A metastatic tumor in the central nervous system may be the first indication of a malignant growth elsewhere in the body. For this reason, if for no other, every patient having an intracranial or intraspinal growth should be subjected to a careful general examination including roentgen examination of the chest and, if necessary, a bronchoscopic biopsy. Even with these precautions, operation on the brain or spine may disclose a secondary lesion.

This is a report of 6 selected cases of carcinoma of the lung in which metastasis to the nervous system had occurred. In a few instances operation was performed without the knowledge that a primary growth was present in the lung. The cases are of further interest because of their clinical course, because of the difficulty in identifying the true nature of the lesion at operation, or because the histologic characteristics observed bore some similarity to those of primary tumors of the nervous system.

REPORT OF CASES

CASE 1: A housewife, aged forty-nine years, registered at The Mayo Clinic on Dec. 24, 1936. She said that for six months she had not been able to keep to the road while driving an automobile, because of failing vision; that four weeks previously she had suffered attacks of severe, sudden, sharp pains in the top of her head, lasting several minutes and recurring four or five times daily; that she had vomited for two days after the onset of these headaches, and that for two days before admission she had experienced continuous bilateral tinnitus. On several occasions there had been visual hallucinations. There had been no symptoms relative to the thorax.

The patient was obese. The results of roentgen examination of the thorax were negative. The tendon reflexes on the right side were slightly more active than on the left, and there was a positive Babinski reflex. Each optic disk was elevated 2 diopters and hemorrhage was present inferior to the right disk. Roentgen examination of the skull showed nothing of significance.

Because of the indefinite symptoms and signs, ventriculography was performed on Dec. 31, revealing a symmetrical internal hydrocephalus, indicating the presence of a subtentorial lesion. This procedure was followed immediately by a bilateral suboccipital craniotomy. A cystic, degenerating tumor was found in the right cerebellar lobe (Fig. 1). Approximately 5 c.c. of glairy mucus were aspirated and the cyst was opened. A nodule situated on its
lateral wall was removed and on microscopic examination proved to be a papillary squamous-cell carcinoma, grade 3 (on the basis of 1 to 4, Broders’ classification).

After operation the temperature gradually rose to 104° F. (40° C.), the pulse to 150 beats per minute, and the respirations to 50 per minute. On Jan. 1, 1937, some cyanosis was noted. On Jan. 2 the patient became delirious and more cyanotic than she had been previously. Roentgen examination of the thorax showed bilateral elevation of the diaphragm and fluid on the right side. On Jan. 5, further roentgen study revealed areas of infiltration and consolidation in both lungs. The patient died on the seventh postoperative day.

At necropsy there was found a tumor, 2 by 3 by 3 cm., in the upper lobe of the right lung near the apex behind the clavicle (Fig. 2). This tumor was at the periphery of the lung and had produced puckering and scarring of the pleura and was seen to surround and infiltrate one of the smaller bronchi. Neither pneumonia nor atelectasis was present in either lung. The lymph nodes at the hilus of the right lung were enlarged and contained tissue similar to the mass in the upper lobe. Another metastatic nodule, 1 cm. in diameter, was situated in the upper lobe of the left lung, separated from the pleura by a narrow zone of normal pulmonary tissue. There was no excess of fluid in any part of the thoracic cavity. Nodules were not found in any other organ in the thorax or abdomen.

![Fig. 1. Escape of thick mucus from a metastatic malignant cyst of the right cerebellar lobe as seen at operation](image-url)

In the right cerebellar hemisphere there remained some neoplastic tissue lateral to the cyst, which had not been removed at operation. This tissue was whitish gray in color, granular, sharply circumscribed but not encapsulated, and lay beneath the meninges, having completely replaced a portion of the cortex of the cerebellum. This was the only tumor found in the central nervous system. There was an internal hydrocephalus, grade 2 (on the basis of 1 to 4). The head of the left caudate nucleus was absent. It was thought at first that this defect was of congenital origin, but the presence of some scavenger cells and hyperplastic astrocytes indicated that it was the result of an old infarction. Most of the cerebral cortex overlying this region of infarction had disappeared. This region included the tip of the temporal lobe and the inferior portion of the precentral gyrus. Other infarcts were not found in the brain and the arteries of the circle of Willis showed only a mild degree of arteriosclerosis.

The neoplasm in the lung proved to be an adenocarcinoma, grade 4, the cells of which showed considerable variation. In some regions they closely simulated squamous cells; in places they assumed a papillomatous form and elsewhere there were definite acini filled with mucus. Even in those regions in which the cells simulated squamous cells, some had in the cytoplasm clear spaces which stained specifically for mucus. Throughout the neoplasm
there was a very marked variation in the size of the cells and of their nuclei; some nuclei were of giant proportions. Mitotic figures were numerous. The most interesting finding was the marked variation in the appearance of the carcinoma from place to place. This held true for the metastatic nodules in the lymph nodes, in the other lung, and in the cerebellum.

In the cerebellar metastasis there seemed to be more mucus, both in the cells and in the stroma, than in the primary growth, and there was much necrosis. The tumor seemed to extend into the surrounding portion of cerebellum along the perivascular spaces in a manner seen in some cases of ependymoma. Many of the vessels, particularly the small veins and capillaries, were dilated. Tumor thrombi were found in some of the small veins, but not in any of the arteries. This relationship to the vessels was observed, also, in the lung. No other carcinomatous lesions were found in the central nervous system on extensive microscopic examination.

Comment: In the roentgenograms of the thorax, the evidence of primary tumor had been concealed by the shadow of the clavicle, and the metastatic lesion in the brain could be located only by means of ventriculography. The neurologic findings were meager, and confusion was introduced by the patient’s left-handedness and the presence of visual hallucinations. Histologically, variations in the type of cells and the general architecture of the neoplasm in different parts of the tumor were interesting. One finding was constant throughout, namely, the presence of large amounts of extracellular and intracellular mucus. A vascular lesion unrelated to the tumor may have accounted for some of the symptoms and signs. The very short history of the illness was in keeping with the malignancy of the tumor.

Case 2: A woman, aged sixty-four years, who registered as a patient Nov. 17, 1932, related that six months previously a pressing pain had appeared in the left side of the forehead and left cheek and that within twenty-four hours this had become intense. There had been, also, paroxysmal, darting pains along the distribution of the second and third divisions of the fifth nerve on the left side. The pain had disappeared abruptly after the removal of a tooth. One month later paresthesias had spread over the distribution of the two upper divisions of the fifth nerve. Three months after the onset of the pain, the patient had thought that a car was parked on the sidewalk; subsequently she had noticed that all objects
appeared double. Two weeks later she had observed that one eye (she insisted that it was the right eye) had turned inward.

Examination of the nasopharynx and of roentgenograms of the head and thorax gave negative results except for evidence of active tuberculosis in the apex of the right lung. The results of examination of the ocular fundi and fields of vision were also negative. The left external rectus muscle of the eye was completely paralyzed. Function of both sensory and motor components of the left fifth cranial nerve was lost. The cerebrospinal fluid, examined elsewhere, was said to have been "very yellow." A diagnosis of tumor of the left gasserian ganglion was made.

At operation, Jan. 17, 1933, the gasserian ganglion was found to be dark and distended as from a recent hemorrhage (Fig. 3). When a small opening was made into the capsule, soft hemorrhagic tissue escaped. Microscopically this proved to be from a malignant neoplasm. The capsule was opened widely and most of the soft mass of tumor was removed. The capsule did not seem to have been invaded by the growth.

After operation all pain was relieved and there was an uneventful convalescence. One course of deep roentgen therapy was given. After the patient had returned to her home, however, she gradually became mentally confused, requiring institutional care. Paralysis of the left side of the face and of the right half of the body developed. Death occurred four months after the operation.

At necropsy it was discovered that the immediate cause of death was bronchopneumonia. There was healed tuberculosis at the apex of the right lung and bronchiectasis was present. In the lower lobe of the left lung, under the pleura, was a gray, discrete, hard nodule 1 cm. in diameter, which proved to be carcinoma. Carcinoma was not found in any of the lymphatic vessels leading to the hilus, nor in the lymph nodes of the hilus. These nodes, however, showed evidence of healed and calcified tuberculous lesions. The larger pulmonary arteries were partially occluded by several adherent and organized thrombi. The only metastatic nodule appeared to be a rounded, soft, glistening, reddish-brown mass, measuring 4 by 5 cm., between the layers of the dura mater in the place ordinarily occupied by the left gasserian ganglion. This mass had extended backward to the posterior surface of the sella turcica; the third cranial nerve was stretched tightly over it and it had compressed the left cerebral peduncle.

The neoplastic lesion in the lung was a papillary adenocarcinoma, grade 2, and contained
much mucus. The cells were large, regular, and distended with mucus; the nuclei were small in comparison with the size of the cells. There were a few mitotic figures and very few hyperchromatic or large nuclei. The neoplasm had all the characteristics of slow growth. The tumor removed at operation, that growing in the lung, and that present in the region of the gasserian ganglion at necropsy were similar to one another. In the last mentioned lesion there were regions of degeneration containing polymorphonuclear leukocytes and some lymphocytes, some old blood clots and blood pigment, and remnants of compressed, degenerating nerve cells and nerve fibers. In a few places the ganglion cells had been replaced by proliferation of endocapular cells.

Comment: In this case the first and most prominent complaint was referable to involvement of the left gasserian ganglion. The primary tumor in the lung was only 1 cm. in diameter at necropsy four months after the cranial operation, and evidence of the tumor had not been detected in roentgenograms of the thorax. Metastatic lesions were not found in the lymph nodes at the hilus of the lung, in the brain itself, or elsewhere in the body except for the left gasserian ganglion. The carcinoma was grade 2, not highly malignant. It was a mucoid papillary adenocarcinoma which probably had taken origin from one of the bronchi. The only neoplasm of the central nervous system that it could be confused with was perhaps papilloma of the choroid plexus. These tumors, however, have never been known to metastasize to the gasserian ganglion or to the lungs. The presence of tuberculosis added to the confusion.

Case 3: A woman, aged fifty-two years, came to the clinic Jan. 11, 1932, because of three jacksonian convulsions. These had begun in the throat and had extended to the left arm and to the left side of the face. The first attack had occurred eight days before registration and had been associated with unconsciousness. Symptoms referable to the thorax were not present.

Roentgenograms of the thorax revealed bilateral pulmonary tuberculosis, slight bronchiectasis, and a circumscribed region at the right second interspace thought to be tuberculosis, although the possibilities of a neoplasm were considered. Roentgen examination of the head showed some changes interpreted as due to old increased intracranial pressure and benign hyperostosis. Examination of vision, of the visual fields for form and color, and of the ocular fundi revealed no abnormality. There were slight deafness on the right side, weakness of the left side of the face which was particularly apparent over the lower part, moderate weakness of the left arm, and some increase in the tendon reflexes of this extremity. Examination of the spinal fluid revealed a protein content of 50 mg. per 100 c.c. and a colloidal gold reaction of 001232100, but the fluid was otherwise normal.

On Jan. 26, 1932, a right craniotomy was performed. Immediately beneath the cortex at the posterior end of the inferior frontal convolution was a hard mass which appeared to be about 3 cm. in diameter. The vessels overlying this were coagulated and a mulberry-like tumor suggestive of a meningioma came into view. It was readily enucleated. A small decompression was made and the wound was closed. A pathologic report of endothelioma was later changed to metastatic carcinoma, probably arising from the lung. Four days after operation the patient died of bronchopneumonia.

At necropsy there was found, surrounding the main bronchus of the lower lobe of the left lung near the hilus, a white mass 3 by 4 cm. in diameter. This had obstructed the bronchus almost completely; distal to the obstruction there was definite bronchiectasis. The upper lobes of the left lung were normal. The lymph nodes at the hilus were enlarged and contained tissue similar to the mass in the lower lobe. In the liver were three nodules, measuring 2 cm. in diameter: one in the left lobe and two in the right. No other metastases were found; all of the metastatic tumor in the brain had been removed at operation.

Histologic examination of the tumor removed at operation showed it to be a papillary adenocarcinoma, grade 2, containing a large amount of mucus both in the cells and free in the stroma. There was an abundance of stroma, some dense, some loose and edematous.
Portions of the tumor were necrotic and contained débris of nuclei and many polymorpho-nuclear leukocytes. There were a few mitotic figures. The cells varied in size because of the presence in some of them of large mucous droplets in the cytoplasm; the nuclei also differed in size and in their position in the cell. The vessels themselves appeared normal and no tumor thrombi could be found in any of them. No other metastatic masses were present in the brain. There was a small metastatic abscess, measuring 7 by 4 by 4 mm., in the right frontal lobe, anterior to the carcinoma. The reaction of the brain around the abscess and around the tumor was one of early glial proliferation, satellitosis, and dilatation and proliferation of the capillaries. The metastatic nodules in the brain and liver and the primary carcinoma in the lung were similar to one another in every respect except that in the lung many veins were dilated and occluded by tumor thrombi. Arteries and arterioles did not contain tumor thrombi.

Comment: This comparatively slowly growing neoplasm arose from the main bronchus leading to the lower lobe of the left lung. The bronchus was completely occluded by the growth and distal to it bronchiectasis was present, probably the result of obstruction by the tumor. The only metastatic nodule in the central nervous system was that which had been removed readily and completely at operation. In all probability, bronchiectasis had been the source of the small metastatic abscess in the right frontal lobe. This abscess was not encapsulated at the time of necropsy.

CASE 4: A man, aged fifty-four years, said that he had been well until seven weeks previous to his examination at the clinic, when he had had a sore throat, coughing, and general malaise. After four or five days he had returned to work and had felt well for about a week. There had then developed transient attacks of vertigo, daily generalized headaches of moderate but increasing intensity, beginning usually between the hours of three and six o'clock in the morning or after exertion, and frequent attacks of vomiting. With the vomiting there had been some staggering.

Roentgenograms of the thorax on March 31 revealed some infiltration of the hilus and upper lobe of the left lung suggestive of recent infection, and on April 4 the roentgenologist mentioned the possibility of primary malignancy. Bronchoscopic examination on April 11 did not show any lesion as far as the opening of the bronchus to the left upper lobe, but it was impossible to pass the tube into this opening. On March 23 there was slight nystagmus on looking toward the right or upward. The ocular fundi were normal in appearance. On April 7 the nystagmus had increased, both disks were choked to the extent of 3 diopters, and there was a moderate degree of ataxia in the movements of the right arm and right leg. While under observation the patient was observed to hiccup. Roentgen examination of the head gave negative results.

Because of the signs of a rapidly progressing intracranial lesion and the difficulty of definitely excluding malignancy of the lung, it was decided to explore the cerebellum. This was done on April 15. At a depth of 5 cm. in the right cerebellar lobe a mass was palpated with a needle. Degenerating tissue was aspirated, examination of which disclosed a malignant neoplasm, grade 4. The patient returned to his home greatly relieved, although the objective findings remained unchanged. He died six months later.

Necropsy disclosed a carcinoma of the main bronchus leading to the upper lobe of the left lung. The tumor measured 4 by 3 cm., had almost completely occluded the lumen of the bronchus near the hilus, and had produced partial atelectasis of the respective lobe. The metastatic process had involved the liver, adrenal glands, and aortic lymph nodes. These metastatic deposits were small, however, compared with that in the right cerebellar hemisphere, about two-thirds of which had been destroyed. This tumor was firmly adherent to the overlying dura mater. A smaller metastatic nodule, measuring 2.5 by 3 cm., was situated deeply in the white matter of the right frontal lobe and another nodule, 7 mm. in diameter, at the upper end of the right postcentral gyrus. All of the metastases in the brain were soft and granular and had a gelatinous appearance, but contained very few regions of degeneration without the formation of cysts. The metastatic nodules in the cerebellum, by
obstruction of the flow of cerebrospinal fluid, had produced an internal hydrocephalus of mild degree.

The very highly malignant neoplasm removed at operation, and impossible to classify definitely at that time, proved to be an “oat-cell” type of adenocarcinoma (Fig. 4). In some regions, under low magnification, the lesion simulated a spindle-cell sarcoma, whereas in others it was like a medulloblastoma. Mucus was not contained in any part of the growth. Radiations from the adventitia of the blood vessels after the manner of primary sarcomas of the brain were nowhere observed. Those cells that simulated medulloblastoma had larger and broader nuclei than the cells of medulloblastoma, the chromatin was less dense and the cytoplasm was not collected at one end in the carrot shape so typical of the cells of medulloblastoma. The nuclei varied slightly in size and there were numerous mitotic figures, but multinucleated cells were not present. There were many regions of necrosis with disintegrating nuclear chromatin and polymorphonuclear leukocytes. Lymphocytes were numerous throughout the neoplasm. The blood vessels did not show abnormal

![Fig. 4. Metastatic Adenocarcinoma in the Brain from a Primary Lesion in the Left Lung: “Oat-cell” Type of Carcinoma, Highly Malignant (Hematoxylin and eosin. × 190.](image)

![Fig. 5. Carcinomatous Cells Growing in Widely Dilated, Thin-walled Veins in the Lung, Showing How Metastasis of Some of These Carcinomas Occurs (Hematoxylin and eosin. × 135.](image)

changes except that the smaller ones were dilated and in some of the thin-walled, dilated veins around the carcinomatous lesion in the lung there were tumor thrombi (Fig. 5). We were unable to identify tumor thrombi or emboli in any of the arteries.

There was little reaction on the part of the brain tissue to the spreading neoplasm. In places the tumor extended into the brain along perivascular spaces; elsewhere the tumor cells were growing directly into apparently normal brain tissue independent of perivascular or other visible spaces. In a few regions around the tumor dilated, thin-walled vessels (probably veins) were seen which showed some proliferation of the endothelial lining. In these same regions there was some degeneration of the brain tissue associated with the presence of scavenger cells, proliferation and hypertrophy of the astrocytes, and even the formation of gemástete glia. The tumor cells of the encephalic metastases were remarkably uniform. Nowhere did they form acini or larger cells, nor did they simulate squamous epithelium.
The primary tumor in the lung and the metastatic nodules in other organs, including those in the brain, were identical with one another histologically. The cells were of the same type, and mitotic figures, regions of necrosis, absence of mucus, and tumor thrombi in the veins were observed in all (Fig. 5).

**Comment:** The "oat-cell carcinoma" was at one time called an "oat-cell sarcoma" because of its close similarity to sarcoma. Of all types of metastatic carcinomas in the brain, this variety is most likely to mislead the pathologist. It was difficult to distinguish the small portion removed through a cannula at operation from a medulloblastoma. The age of the patient, the site of the metastatic lesion, the variability in size of cells and nuclei, and the presence of many mitotic figures are helpful in making the distinction.

**CASE 5:** A clothing merchant, aged forty years, registered at the clinic on Feb. 19, 1936. On Feb. 5 he had experienced a dull frontal headache; on Feb. 9, right facial paralysis and diplopia accompanied by external strabismus of the right eye. After Feb. 12, the left eyeball refused to turn inward, upward, or downward. On Feb. 15, a dull ache developed over the sacrum and along the posterior aspect of both legs. There had been no cough or other symptoms referable to the chest.

Physical examination gave essentially negative results. Roentgenograms of the thorax on Feb. 20 revealed a large circumscribed region of increased density in the right hilus at the level of the third rib, regarded as probably made up of calcified nodes, although the presence of tumor could not be ruled out. Vision was somewhat reduced by haziness of both corneas and lenses, but the optic disks appeared to be normal. There was complete ptosis on the right and partial ptosis on the left. Lateral movements of the left globe were normal; of the right globe, moderately restricted. Otherwise the right globe was immobile, and the left almost so. Reaction of the left pupil to illumination, both direct and crossed, was impaired; neither pupil reacted to accommodation and convergence was absent. The right side of the face was completely paralyzed. Occasional fibrillary tremors of both lower extremities were observed. The right corneal reflex was absent. The right patellar reflex was absent and there was a positive Babinski sign on the left. Lasègue's sign was moderately positive on both sides. Roentgen studies of the skull showed it to be normal.

A diagnosis of neuritis was made, but with recurrent misgivings. On Feb. 22 slight weakness of the muscles of the left side of the face developed and the patient complained of steadily increasing pain in the sacral region. On Feb. 27 there appeared weakness of the muscles of the pelvic girdle and thighs, and both patellar reflexes were absent, though the Achilles tendon reflexes remained normal. The muscles of mastication were also becoming weak. The weakness increased steadily. On Feb. 29 there was marked weakness of the quadriceps muscle on the right with moderate weakness on the left. On March 8, all muscles supplied by the left facial nerve were weaker than previously. Sensory disturbances were not present. The Achilles tendon reflexes on both sides were now lost. The results of examination of the ocular fundi remained negative throughout the remainder of the illness. On March 18 the patient complained of severe shooting pains in both legs. Thereafter numbness of the legs and of the sacral region developed, but anesthesia could not be demonstrated objectively. Roentgen therapy gave marked relief. The roentgenologic report of March 29 was "infiltrating lesion in the right hilus with marked elevation of the diaphragm; primary lesion of the bronchus." The situation precluded bronchoscopic visualization. The course of the illness was progressively downhill and during the two weeks before death a bulbar palsy and a palsy of the right vocal cord developed. The patient died April 13.

Six spinal punctures were made between Feb. 21 and March 31. The pressure never exceeded 13 cm. of water with the patient lying on his side and response of the pressure to jugular compression did not indicate obstruction. The fluid was clear and at first colorless; later it became yellow. On four occasions a pellicle formed. The test for tryptophane was positive. Mycobacterium tuberculosis was not found. Once the fluid coagulated spontaneously. Nonne's test gave positive results. The content of protein fluctuated between 160
and 1000 mg. per 100 c.c. On one occasion the content of sugar was 39 mg. per 100 c.c. and the chlorides 676 mg. per 100 c.c. The number of lymphocytes varied from 36 to 505 per cubic millimeter and the neutrophils from 0 to 32 per cubic millimeter. The result of the colloidal gold test was 0.00011110 on two occasions.

At necropsy a tumor was found surrounding the main bronchus near the hilus of the right upper lobe. This mass measured 4 by 4 by 3 cm. Several nodules about 3 mm. in diameter were found in the lower lobe of the right lung. There were no masses in the middle lobe. In the left lung there were several small nodules, each measuring about 2 mm. in diameter, in the lower lobe, but none in the upper lobe. Many enlarged lymph nodes at the hilus of the right lung contained tumor tissue. About 500 c.c. of fluid were present in the right pleural cavity and about 200 c.c. in the left. A tumor about 3 mm. in diameter was found in the wall of the stomach and another, 3 by 3 by 2 cm., on the mesenteric border of the ileum 24 cm. proximal to the ileocecal valve. There were also metastatic lesions in both adrenal glands, the mass in the right one being 2 cm. in diameter and that in the left 5 cm. in diameter. No metastatic lesions were found in any of the other organs except the central nervous system. Carcinoma was not present in the meninges or in the substance of the brain or spinal cord except in the floor of the third ventricle, which was thickened and opaque, but almost all the cranial nerves and most of the roots of the spinal nerve, particularly the dorsal ones and their ganglia, were enlarged. The gasserian ganglia were as much as fifteen times the normal size (Fig. 6).

![Image of normal and abnormal cranial nerves](image-url)

**Fig. 6. Specimens of Normal and Abnormal Cranial Nerves**

Normal nerves are represented in the upper row and those which have become involved by metastatic lesions are shown in the lower row.

On histologic examination the neoplasm in the lung simulated a lymphosarcoma but was found to be a carcinoma made up practically entirely of small round cells. The cells and their nuclei were larger than those of a lymphosarcoma and the cells occasionally formed incomplete acini. Other evidence of glandular formation was not found, and mucus was nowhere present. There were numerous mitotic figures, but there was very little variation in the size of the cells or of their nuclei. Neither giant nuclei nor giant cells were present. The carcinoma in the lung and in the lymph nodes of the hilus showed a remarkable tendency to invade the neighboring veins. In the central nervous system the tumor cells were identical with those seen in the lungs, namely, small round cells growing without any evidence of inhibition. These cells were growing freely in the nerve roots and extended in rows between the fibers. Many myelin sheaths and nerve fibers had been destroyed. The neoplasm had invaded the gasserian and dorsal root ganglia. Many ganglion cells survived even in the midst of neoplastic tissue, but many were observed to be in the process of degeneration.

Proliferation of the capsular cells did not occur. Very few tumor cells were seen in the subarachnoid space. A large mass of tumor cells invaded the floor of the third ventricle and
there the nerve cells had been destroyed and some of the glial cells had become degenerated. The neoplasm spread along the perivascular spaces for some distance beyond the main mass of the tumor. Tumor cells surrounded some nerve cells, after the manner of satellite cells. In the nervous system there was a greater variation in the size of the tumor cells and of their nuclei than in the primary growth in the lung, but multinucleated giant cells or giant nuclei were not present. In many places there were tumor thrombi in the veins and occasionally in some of the smaller arteries, but this was believed to be the result of invasion rather than of tumor emboli from the lung.

The peripheral nervous system beyond the dorsal root ganglia was free from metastasis, but there was marked degeneration of the myelin sheaths and axis cylinders associated with proliferation of the cells of the sheath of Schwann. These changes were similar to those observed in cases of neuronitis by Gilpin, Moersch, and Kernohan.

Comment: In our experience this is a unique type of tumor, both in the distribution of the metastatic lesions in the nervous system and in their histologic appearance. They closely simulated lymphosarcoma, but dissemination in the central nervous system was not like that of lymphosarcoma and the cells and nuclei were larger than those of lymphosarcoma. Only occasionally was there an attempt to form acini and, as in cases of "oat-cell carcinoma," mucus was not present. Presumably, this neoplasm arose from the indifferent cells of the bronchi, but did not form "oat cells." The degeneration of the peripheral nerves was identical with that found in neuronitis, and this was considered the diagnosis for a time, but the persistent pain, the extensive involvement of the oculomotor nerves, the large number of cells in the spinal fluid, and the enigmatic mass in the thorax furnished grounds for many a period of uncertainty.

Case 6: A retired contractor, aged fifty-six years, presented himself at the clinic June 8, 1937, because of increasing weakness in the lower extremities. For ten or twelve years he had had a recurrent productive cough which had kept him from work. Six weeks before registration he had experienced a gradually increasing sensation of heat in the left lower extremity, and three weeks before registration, a band-like sensation around the toes of the right foot and progressing weakness of the right lower extremity. Ten days before coming to the clinic, anesthesia of the genitalia and incontinence of urine had appeared.

The principal findings included weakness of the lower extremities, which was slight on the left and somewhat more prominent on the right. The associated signs indicated involvement of the upper motor neurons. There were moderate impairment of appreciation of pain and great impairment of appreciation of temperature below the left groin, with retained sensibility in the perianal region, failure to appreciate vibratory sensibility over the iliac crests and malleoli, and a moderate degree of impairment of appreciation of movement of the toes. There were 250 c.c. of residual urine. Examination of the spinal fluid gave negative results save for evidence of a partial block on jugular compression and a content of 50 mg. of protein per 100 c.c. of spinal fluid.

By June 14, six days after registration, complete paraplegia was present. On the left side there was cutaneous sensory impairment, having an ill-defined upper border in the distribution of the eleventh thoracic segment, increasing in intensity caudally to the distribution of the second lumbar segment, below which there was complete anesthesia. On the right side there were slight impairment of tactile sensation and great impairment of perception of pain and temperature. The anal sphincter was relaxed. Roentgenograms disclosed slight hypertrophic arthritis of the lower cervical and thoracic spine and marked narrowing of the intervertebral spaces between the fourth and fifth lumbar and between the fifth lumbar and first sacral vertebrae. Roentgenograms of the thorax were interpreted as revealing bilateral bronchitis, an old lesion at the level of the second rib on the right side anteriorly, probably lymph nodes, and a Ghon complex on the left at the level of the third rib. The sedimentation rate ranged from 45 to 125 mm. per hour.

On June 16 the introduction of lipiodol into the spinal canal disclosed two protruded
intervertebral disks, which were too low to account for the symptoms and signs, but evidence of blocking at higher levels was lacking. By June 21 there was complete loss of sensation below the distribution of the eleventh thoracic segment. While the patellar reflexes became increased, the Achilles tendon reflexes disappeared. On June 25 roentgenograms of the thorax revealed a localized region of dense infiltration near the right hilus, supposedly due to an inflammatory process or to localized bronchiectasis.

On Aug. 4, roentgenograms of the spine disclosed a tumor of the ninth dorsal vertebra. Roentgenograms of the thorax showed infiltration of the right hilus and right fourth inter-space and a minimal, old, coarse, narrow, fibrotic lesion at the level of the second rib on the right and some pleural thickening. It was suggested that a primary carcinoma of the bronchus be ruled out. The finding of one acid-fast bacillus in one of several specimens of sputum constituted presumptive evidence that tuberculosis was present, but an absolute diagnosis could not be made on this evidence alone. The story was suggestive of asthmatic bronchitis, possibly associated with bronchiectasis.

After July 18 the patient at times became somewhat disoriented and complained of headache and fatigue. Occasionally there was a slight elevation of temperature, which became more or less constant. On July 27 there were discovered some diminution in sensation over the first division of the fifth cranial nerve on the right and impairment of upward gaze. Frequent hiccoughing and dysphagia appeared.

On Aug. 4 there was some weakness of the right arm and of the right side of the face. A hard nodule was discovered under the right mandible. At this time a diagnosis of carcinomatous metastasis was made. Bronchopneumonia developed and the patient died on Aug. 9 after sixty-three days in the hospital.

At necropsy a carcinoma was found in the middle lobe of the right lung. The tumor was 3 cm. in diameter and was situated at the hilus of the lung, extending along the bronchi to the middle lobe. The bronchi were obstructed by the growth and distal to the obstruction there was a severe degree of bronchiectasis. Metastasis had occurred to the lymph nodes at the hilus, to the anterior mediastinum, the pancreas, kidneys, and adrenal glands. Permission to examine the brain could not be obtained. There was, however, a region of softening 4 cm. in length involving the lower thoracic portion of the spinal cord. This portion was swollen and necrotic, and the normal markings were absent on cross section.

Microscopic examination of the carcinoma in the lung showed it to be made up of a pleomorphic type of cell, although occasionally the cells were growing in an acinar arrangement. The metastatic nodules contained cells of similar type, and mucus was not present. In the middle of the necrotic portion of the spinal cord a very small mass of cancer cells was found, not more than 2 mm. in diameter. The surrounding tissue of the cord was necrotic; all myelin sheaths and axis cylinders had disappeared and were replaced by large scavenger cells (compound granular corpuscles). The microscopic appearance of this region simulated very closely that which has been described by Moersch and Kernohan as acute ascending necrosis of the spinal cord. We were unable to find any blood vessels occluded by cancer cells or other material, yet in all probability metastasis occurred by way of the blood stream. No other metastatic lesions were found in the spinal cord or meninges.

Comment: This is a unique case in that the metastatic process which involved the spinal cord was suspected to have originated in the lung before the primary growth in the lung was discovered. Metastasis produced an extensive region of necrosis many times larger than the mass of cancer cells. Metastatic lesions in the central nervous system are sometimes surrounded by a zone of necrosis, but we have never seen such a region of necrosis, many times larger than the metastatic mass itself, as in this instance.

Comment

Metastasis of carcinomas to the central nervous system is not uncommon. The primary lesion is usually found, however, before any neurosurgical inter-
ference is undertaken and is usually considered adequate reason for not attempting such measures. Experience probably justifies this course in most instances. Usually there are metastases elsewhere. When the tumor in the brain is the only demonstrable metastatic lesion and the primary carcinoma is small and slowly growing, enucleation of the cerebral lesion may be justified.

Metastasis to the central nervous system may take place from almost any organ of the body, but the lung is the most frequent primary seat of such a neoplasm. In the Mayo Clinic it has become a routine procedure in the neurologic department to obtain roentgenograms of the thorax in all cases in which a neoplasm of the central nervous system is suspected. This procedure has disclosed most carcinomas of the lung and in doubtful cases bronchoscopic examination has usually settled the question. In spite of these precautions, some patients are mistakenly operated on for primary tumors of the brain, as the examples cited demonstrate. The primary tumor may be hidden by the shadow of the clavicle, the heart, or the hilus of the lung. Often pulmonary symptoms are not present. In one case tuberculosis was considered and subsequently healed tuberculosis was found with a carcinomatous lesion growing nearby.

Some other phases of carcinoma of the lung and its cerebral metastatic lesions deserve comment. It is now generally accepted that all carcinomas of the lungs are bronchogenic in origin. Four types of cells line the normal bronchus, but most carcinomas arise from the small cells wedged in between the base of the larger ciliated and goblet cells. These cells have the power of differentiating into ciliated cells, goblet cells, or mucus-containing cells, and into epithelium that simulates squamous cells. When the potentialities of these cells are realized, it is possible to explain the various types of carcinoma that can originate in a bronchus. It is remarkable that more carcinomas have not been described in which the several varieties of cells and types of architecture have been emphasized.

Much emphasis has been placed on the rapidity of growth, the number, situation and early occurrence of metastatic lesions, and the site of the carcinoma in the hilus and periphery of the lung itself. A finding common to all of our cases was that of tumor thrombi in the veins of adjacent bronchi or pulmonary tissue. There has been some difference of opinion as to whether metastasis of carcinoma occurs from the lungs to the brain by way of the lymphatic vessels or by means of tumor thrombi and emboli through the blood stream. The consensus of opinion seems to be that the blood stream is the most likely route and most of our findings corroborate this. We must admit our failure to find more than one small artery dilated and filled with a tumor embolus at the site of a metastatic nodule in the brain, but it is likely that this evidence is soon destroyed by the growth itself.

Case 5, in which multiple invasion of the nerve roots and ganglia occurred, is a possible illustration of dissemination of carcinoma from the lung to the nervous system by way of lymphatic vessels, which is one reason for its inclusion in this series. It was, however, the only case in our series in which such a process was observed. On the other hand, in case 2, in which there was one small carcinoma 1 cm. in diameter in the periphery of the lung, metastasis did not involve the lymph nodes at the hilus, the lymph nodes in the neck, or
any other tissue except the left gasserian ganglion. This is suggestive of dissemination by way of the blood stream. All types of carcinoma of the bronchi may cause metastasis to the central nervous system except the basal-cell type, which frequently is referred to as an adenoma of the bronchus. Tumors of this variety seldom lead to metastasis and are of a low grade of malignancy.

It is important to distinguish metastatic carcinomatous lesions of the central nervous system from primary neoplasms of the brain. Sometimes such distinctions are made with difficulty, particularly when very small portions of tumor have been removed at operation. It is especially difficult at times to differentiate the so-called oat-cell variety from medulloblastoma unless the age of the patient and the situation of the growth are taken into consideration. If, however, attention is given, also, to the number of mitotic figures, the size of the nuclei, and the amount and arrangement of the cytoplasm, a correct diagnosis can be made. In case 2 it was necessary to rule out the so-called sheath neuroma. The tissue removed at operation bore superficial resemblance to the sheath neuroma of the gasserian ganglion described by Learmonth and Kernohan. Occasionally one of these metastatic carcinomatous lesions must be distinguished from a lymphosarcoma or from a primary sarcoma of the brain. Indeed, the oat-cell carcinoma of the lung was considered to be a sarcoma until the error was pointed out by Barnard, and if such a primary carcinoma in the lung is undiscovered, the trap is especially well laid.

The reaction of the brain to the presence of a metastatic carcinomatous nodule is not specific. It varies from case to case and even in different portions of the periphery of the same lesion. Degeneration, proliferation or hypertrophy of the astrocytes may occur, or they may form gemästete glia. If there are destruction and degeneration of the brain tissue, there are an increase in the number of microglia and the formation of scavenger cells. The oligodendroglial cells undergo acute swelling and disappear. The blood vessels seem to increase in number, but this may be more apparent than real, since all of the vessels, especially the smaller ones, are dilated. Sometimes there is definite proliferation of the endothelial cells of the intima of these dilated vessels.

References