Spectrum of symptomatic brain-stem metastasis

BENNETT M. DERBY AND RODOLFO L. GUIANG

From the Department of Neurology, New York University School of Medicine, and the Neurology Service, Veterans Administration Hospital, New York, N.Y., U.S.A.

SYNOPSIS Three cases are presented which depict the spectrum of neurological disability attendant on intra-axial brain-stem metastases, ranging from fulminant decline to a more leisurely and less disabling course. The rarity of primary glioma of brain-stem compared with brain-stem metastases in a general hospital population in the age group from 50 years and over is emphasized. Clinical deficit, certain ancillary findings, and response to therapy do not serve to separate brain-stem glioma from secondary brain-stem metastasis. The primary tumour may not be apparent when central nervous system symptoms appear or even for as long as two years after. It is recommended that the diagnosis of primary brain-stem glioma in the middle-aged adult be provisional and increasingly tentative over the age of 50 years.

Nothing is written about the natural history of metastases to the brain-stem. Although texts and reviews provide familiar data on secondary tumour deposits within the cerebral hemispheres, symptomatic brain-stem metastases are tacitly acknowledged to be unusual and quickly lethal, and to present no significant problem in recognition. The swift evolution of predominant intramedullary brain-stem dysfunction in our original patient with a known primary malignancy was therefore of limited interest.

Subsequent experience with two more patients provided surprising exceptions to the general idea of the longitudinal picture of metastatic brain-stem disease. These demonstrated the ease of confusing intra-axial brain-stem metastasis with primary brain-stem glioma when there is no evidence for a primary site or lesions elsewhere. They forcefully draw attention to the mild clinical disability and relatively benign course of some cases. The first typical case is contrasted with the more prolonged course of the others to illustrate the clinical spectrum. The prevalent assumption that symptomatic brain-stem metastasis is rare will be examined.

CASE 1

F.K. (090-05-5523) A-190-71 A 57 year old man who smoked three packs of cigarettes daily was admitted to another hospital because of daily haemoptysis of two weeks' duration and increasingly productive cough and dyspnoea in the previous six months. Bronchoscopy, scalene node biopsy, and right upper lobectomy for a pulmonary mass gave the histological diagnosis of undifferentiated lung carcinoma. Radiotherapy (3,000 rad) was given to the upper lobe of the right lung and mediastinum. He remained asymptomatic for seven months when left-sided headaches, nausea, and vomiting began. Despite corticosteroid therapy these persisted and two months later right-sided weakness appeared. Speech became slurred, and progressive lethargy and general weakness prompted admission.

Examination disclosed mild generalized confusion, slow and at times explosive speech, and bilateral one-dioptre papilloedema. Visual fields were full. Horizontal conjugate gaze palsy to the left was noted on visual cue and on cold caloric tests. Pain sensation in the left face and cornea was diminished. The jaw deviated to the left on mouth opening. Left peripheral facial palsy was evident. Gross hearing and Weber and Rinne tests were normal as were the functions of the palate, uvula, tongue, gag response, and swallowing. Right-sided weakness of the limbs with sparing of the right half of the face was combined with a left-sided intention tremor and heel-to-shin ataxia. Deep tendon reflexes were brisker on the right than left and the right plantar response was extensor. Pain sensation in the right trunk was diminished from the neck down,
including the right limbs, with variable impairment of vibratory sense in the distal parts.

Brain scanning demonstrated a large area of increased uptake of isotope in the left posterior frontal and anterior temporal regions. Routine chemical analyses and blood count were normal. In the chest radiograph a poorly defined soft tissue density widened the right upper mediastinum. Corticosteroids were given at higher dosage. After two weeks of progressive unresponsiveness, right limb weakness and general debility, the patient died.

Postmortem examination showed no tumour in the remaining portions of the lungs or elsewhere in extracranial organs, and bilateral lower lobe aspersion pneumonia was found. The brain weight was 1 650 g and the overall appearance was quite full with bilateral tentorial indentation marks but no herniation. The left cerebellar tonsil was three times larger than the right. There was anterior cingulate herniation from left to right. The left cerebral dural leaf was adherent to the left frontal superior convexity, overlying a large subcortical mushy tumour mass. The entire left cerebral hemisphere was enlarged by white matter oedema extending down through the internal capsule and striatum but not into the midbrain. The third ventricle was shifted and bowed from left to right. The left lateral ventricle was paradoxically dilated and the right was severely crimped. Another brownish mass in the posterior temporal lobe elevated the floor of the posterior horn of the left lateral ventricle.

Occupying the left brain-stem tegmentum, from the mesencephalopontine to the pontomedullary junctions, was a brownish yellow haemorrhagic mass (Fig. 1). The oral half of the basis pontis was tilted, the right basis drooping below the left. The transition from the aqueduct to fourth ventricle, and the oral portion of the fourth ventricle were virtually blocked by tumour mass which thrust up and elevated the vermis. This mass extended across the tegmental midline into the right side at all pontine levels and also extended into all three cerebellar peduncles on the left, exciting yellowish oedema in the left cerebellar centrum medullare. A soft yellow mass expanded the cortex of the inferior medial left cerebellar hemisphere corresponding with the external tonsillar enlargement.

Microscopy revealed solidly arranged tumour cells with large irregular and vacuolated cytoplasm and hyperchromatic nuclei. Areas of necrosis and papillary proliferation in the tumour were surrounded by oedema and moderate astrocytic proliferation.

COMMENT This illustrates one end of the spectrum of metastatic intramedullary brain-stem disease wherein death occurred only three months from the onset of the first symptoms of intracranial disease. On a background of known lung cancer of undifferentiated type, subacute progressive intracranial hypertension was soon followed by focal disorder of long motor, sensory and cerebellar tracts and multiple cranial nerves. Despite clinical phenomenology pointing directly to the brain-stem, brain scanning showed a hemisphere lesion which otherwise would have been unsuspected, and provided evidence of multiple lesions. Within two weeks of hospitalization death occurred with relentless intracranial hypertension.

CASE 2

J.C. (065-18-5724) A-19-72 A 49 year old man presented with three months of increasing unsteadi-
ness, frequent falling to the right, and numbness of the right hand. Later, he had left frontal headache and noticed a tendency of his eyes and tongue to deviate to one side. On examination, he was alert and slightly dysarthric. The eyes were tonically deviated to the right and he had to turn his head en masse to the left in order to see in front. Pupils were equal. He could not hear well with the right ear and used the left ear for telephone conversations. On caloric tests, there was no response in either ear. He could stand by himself but was ataxic on walking. In addition to mild weakness of the right limbs, their individual movements were dysmetric.

Chest and skull radiographs were negative. The only CSF abnormality was a protein of 0.74 g/l. On EEG, minimal slowing was noted more on the left. A brain scan showed isotope uptake in the left occipital area. Brachial arteriography showed shift of vermis veins to the right. A posterior and left-to-right shift of the fourth ventricle was noted on pneumoencephalography with a filling defect of its inferior portion. The rest of the ventricular system was minimally enlarged. The conclusion was a large brain stem glioma. Total irradiation of 5 000 rad and corticosteroids were given. On discharge three months later additional findings were an extensor plantar response and hyperactive reflexes on the right, and decrease in touch and position sense in the right hand. Adduction of the right eye was nearly normal, leaving a left abducens palsy. There was also weakness of the left upper and lower facial muscles.

Episodes of undiagnosed abdominal pain occurred four and six months later. Chest films now disclosed infiltration of the upper lobe of the left lung and serum alkaline phosphatase had increased to 95 u/l.

Nine months after discharge he was again admitted for 10 days for worsening of gait and headache. Neurological examination was unchanged. Corticosteroids were continued and he was discharged. Admission for a fortnight followed one month later occasioned by increasing headache, numbness of the right side, and inability to walk. Abnormal blood values were a leucocytosis of 17.5 x 10^9/l; serum aspartate aminotransferase of 52 u/l; LDH of 3 330 u/l; and alkaline phosphatase of 265 u/l. During pneumoencephalography he became unconscious with stertorous breathing. The ventricular system was enlarged from the previous study. The fourth ventricle was shifted posteriorly but not laterally and the basal cisterns were encroached upon. With administration of corticosteroids, headache waned and he was discharged unable to walk.

At home, the headache soon returned and repeated vomiting appeared. On readmission 12 days later, he was unresponsive to verbal stimuli and partially responsive to pain; the right optic disc was blurred and respirations were shallow and irregular. Constricted pupils dilated 12 hours later and he died.

At necropsy primary tumour was found in the upper lobe of the left lung, with implants in ribs, vertebral bodies, liver, spleen, and mediastinal lymph nodes. The brain weight was 1 430 g. The cerebral hemispheres were equal in size and there was no herniation. The left frontal pole was covered by a mucoid greyish deposit. Underneath was a large necrotic tumour mass. Scattered throughout the

FIG. 2 In lower pons both sides of the tegmentum are infiltrated with tumour and expanded, pushing the floor of the fourth ventricle into the vermis.
remainder of both cerebral hemispheres were 16 necrotic, haemorrhagic tumour nodules, up to 2.5 cm in diameter. Variable amounts of white matter oedema surrounded these lesions, so uniformly scattered that there was no internal shift of the brain and the ventricular outline was normal. Both cerebellar tonsils were symmetrical. From upper pons to pontomedullary junction, whitish grey mass occupied the tegumentum with largest diameter at the midpons (Fig. 2). This expanded the floor of the fourth ventricle upward closing the lumen by 50%. It compressed the basis pontis downwards, the middle peduncle laterally and also extended across the midline to the right. The histology in all deposits revealed well differentiated adenocarcinoma similar to the primary tumour in the upper lobe of the left lung. Tumour cells infiltrated the meninges diffusely and extended into the upper spinal cord.

COMMENT A metastatic brain-stem and cerebral malignancy was mistaken for primary brain-stem glioma. The onset was characterized by simultaneous mild intracranial hypertension and symptomatic focal disease of the brain-stem. The progression was uneven and irregular, punctuated by intermittent worsening of the intracranial hypertension and terminating in hydrocephalic crisis. The failure to recognize metastatic intra-axial brain-stem disease, especially when there was other circumstantial evidence of metastases provided by the brain scan and later by abnormal blood chemistry values, is noted. We wish to underline the overall course, from the onset of the first intracranial symptoms to death, of a relatively long 1½ years, assuming a tempo intermediate between that of case 1 and case 3.

CASE 3

J.E. (063-01-6421) A-117-73 Eight months previously this 59 year old man noted the insidious onset of generalized headache, lightheadedness, and wobbly unsteadiness. One month later his legs gave way transiently while he was about to climb a flight of stairs. Several days later, he noted clumsiness and numbness of the right limbs. From then on he noted that his right eye often ‘twisted in’ and vision became blurred. Speaking became slowed. Ringing in the left ear also appeared for the first time, while that in the right ear, present for 22 years, worsened. His wife noticed increasing emotional lability. He lost 13.6 kg (30 lb) in four months from poor appetite. In two hospitalizations elsewhere he was treated for hypertension. CSF examination and EEG were normal, and cerebral arteriography was said to show atherosclerosis.

On admission he was alert and aware. Speech was slurred but not aphasic. He walked straight with a wide base without veering. Outstretched fingers showed a piano-playing tremor; hand writing was a scrawl. Individual limb movements were strong and accurate. Reflexes were symmetrical and the plantar responses flexor. Decrease of pain sensation on the right was the only sensory abnormality. Optic discs were unremarkable. Pupils were equally reactive to light and accommodation. Vertical conjugate gaze was full and without nystagmus. Horizontal conjugate gaze to either side was absent, even with cold caloric test; this manoeuvre provoked only ocular convergence with miosis and without nystagmus.

Dizziness, ataxia of gait, intermittent ocular convergence spasms and horizontal conjugate gaze palsy remained. Skull and chest films were normal. Several CSF examinations revealed an average opening pressure of 200 mm of water with clear acellular fluid. The protein was consistently 0.9-1.2 g/l. EEG was normal and brain scan was negative. Pneumoencephalography performed twice showed failure of filling of the fourth ventricle while the basal cisterns and the rest of the ventricular system were normal. Cerebral arteriograms demonstrated a highly vascular intra-axial brain-stem mass. The clinical conclusion was brain-stem glioma. The patient was discharged clinically stable on corticosteroids.

At home a few months later, dizziness and unsteadiness increased with more frequent headache, nausea, and vomiting. On readmission four months after the first admission the optic discs were flat. He was irritable and could no longer stand unsupported, but sat straight. Strength in all limbs remained good but movements were slower than before. The ocular convergence spasm could no longer be provoked on caloric testing. Bilateral horizontal gaze palsy with intact vertical gaze and normal pupils remained. A brain scan was again normal. Carotid angiography suggested ventricular enlargement. On ventriculography, a brain-stem mass projecting into the fourth ventricle was found. A course of intravenous chemotherapy with 1,3-bis(2-chloroethyl)-l-nitrosourea and radiation to the head were given and corticosteroids were increased.

In the ensuing months attempts to taper maintenance doses of corticosteroid resulted in prompt reappearance of headache, nausea, and vomiting. Dizziness and truncal ataxia with inability to stand persisted. He sat well in a wheelchair and could wheel himself skilfully. Speech remained minimally dysarthric; optic discs remained flat; and the bilateral horizontal conjugate gaze palsy was unchanged.
Periodic chest films and liver scans failed to show evidence of metastatic lesions.

One year after the second admission, two years after the first neurological symptoms, gross haematuria occurred and a mass was palpated in the right upper quadrant of the abdomen. Intravenous pyelography and renal arteriography demonstrated a highly vascular right renal mass. Right nephrectomy demonstrated clear cell carcinoma of the right kidney with invasion of the renal vein and adrenal gland. The revised diagnosis was brain-stem metastasis from primary carcinoma of the kidney. Five months later haemorrhagic ascites appeared. He remained neurologically stable with minimal dysarthria and dizziness, mild finger clumsiness, unobtrusive but intermittent mental irritability and severe standing ataxia but with adequate independence in a wheelchair. Eight months after nephrectomy consciousness slowly deteriorated and he died.

Necropsy disclosed multiple small yellowish tumour nodules within the liver, both lungs, pleura, diaphragm, omentum, mesentery, and the serosal surfaces of the small intestine. Hilar, paratracheal, mesenteric, and retroperitoneal lymph nodes were involved. The brain weighed 1410 g. The lateral ventricular system was mildly dilated. No tumour was found in the cerebral hemispheres on gross and microscopical examination.

There was firm bulging of the anterior vermis and mild widening of the basis pontis. Occupying the tegmentum from uppermost pons into upper medulla was partly firm and partly haemorrhagic necrotic tumour whose sharply marginated mass severely narrowed but did not fully obstruct the fourth ventricle (Fig. 3). Superiorly, the tumour spared the left tegmentum, and in the middle pons it crossed the midline and completely infiltrated the tegmentum into the upper one-third of the medulla, incorporating the medial longitudinal fasciculus, lemnisci and multiple nuclear areas. In the middle pons the tumour extended only a short distance inferiorly and the major defect was one of compression and bowing of the upper basis pontis. At all levels the tumour was surrounded by yellowish oedema extending partially into the middle cerebellar peduncles. Microscopically the tumour was composed of sheets of large clear cells identical with those seen in the other organs.

**COMMENT** Here is illustrated the most prolonged course (2½ years) and benign disability from metastatic intra-axial brain-stem malignancy. The mode of onset, with nearly simultaneous occurrence of mild signs of intracranial hypertension and focal disease, is similar to the previous two cases. The relatively restricted degree of clinical disability, amenability to relief, and then stability for long periods is remarkable. Again, the initial confusion with a primary brain-stem glioma is obvious. Especially noteworthy was the absence of other cerebral metastases. The deposit in the brain-stem was the sole involvement of the nervous system and would have been amenable to surgical relief had it been located elsewhere. Nonetheless, multiple somatic metastases limited survival.
DISCUSSION

Brain-stem metastases are not frequent. In a dozen necropsy studies of central nervous system metastases where brain-stem involvement was specified (Hunter and Rewcastle, 1968) the overall incidence was nearly one in 10 (8%), but there had been no correlation with size or clinical manifestations. Miliary metastases are microscopic, none large enough to produce dysfunction. In cases with gross deposits, brain-stem lesions are overshadowed by the manifestations of masses within the cerebral hemispheres. Thus specific clinical pictures due to intra-axial brain-stem metastasis are considered rare.

Brain-stem glioma in the adult, on the other hand, is invariably symptomatic and is amply recorded (Barnett and Hyland, 1952; Cooper et al., 1952; Netsky and Strohos, 1952; White, 1963; Golden et al., 1972). Comparative figures are not available relating the incidence of symptomatic metastasis to that of glioma in the brain-stem. One report of brain-stem glioma covering the period 1930–50 (Barnett and Hyland, 1952), however, is from the same institution reporting a study of brain-stem metastases during the period 1932–66 (Hunter and Rewcastle, 1968) and the figures are broadly comparable. In a 34 year period, 45 brain-stem metastases were found on pathological study, but in only eight was neurological abnormality retrospectively considered a direct result of the brain-stem lesion. During a 20 year period, 32 primary brain-stem gliomas were found. The impression is that brain-stem gliomas are manifestly more frequent than symptomatic brain-stem metastases.

In contrast, only one brain-stem glioma has been seen at this unit in a 10 year period when 150 gliomas elsewhere have been diagnosed at surgery or necropsy. Three cases of clinical brain-stem metastasis presented within a one year period. This experience led us to suggest that the rarity of clinical brain-stem metastasis relative to brain-stem gliomas may be more apparent than real. The impressive series of primary brain-stem gliomas from the Neurological Institute of New York (White, 1963) encompassed a 31 year period in a selective referral centre. The medulla oblongata glioma series from the Mayo Clinic (Cooper et al., 1952) was likewise derived from another major referral centre. Similarly, a midbrain glioma report (Netsky and Strozos, 1952) was gleaned from the files of a chronic neurological hospital serving the entire New York City area. Specialized centres preferentially receive glioma material, not an accurate reflection of general experience.

The patient population at this hospital consists mainly of veterans of the Second World War in the fifth decade of life onward. Experience is therefore based on the general care of later middle-aged males, with a heavy incidence of carcinoma of the lung and other organs. The age span of series of primary stem glioma is different. Only one fourth of the 44 patients of White (1963) were over 50 years of age; in eight adults of the group of Golden et al. (1972) the age span was 30 to 56 years; and of nine adults in the report of Cooper et al. (1952) only one was over the age of 50 years. Primary brain-stem gliomas display a bimodal age distribution, showing one very much larger group in childhood and another much smaller group in adults. The adult group shows a peak at age 45 years (Golden et al., 1972) with a sharp decline thereafter. In an extensive review of the age incidence of intrinsic tumours of the brain-stem occurring in 105 cases from the literature, Bucy and Keppler (1959) published a bar graph documenting the paucity of cases above the age of 20 years, accounting for only 13%. Only one case was over the age of 50 years. The curve of incidence thus falls rapidly at the ages when the frequency of metastatic carcinoma is swiftly rising. Two of our three patients were in their late 50s and one was 49 years old. The bulk of the cases of Hunter and Rewcastle (1968) were over 50 years of age. In isolated reports, the age of one was 52 years (Netsky and Strohos, 1952) and the other 66 years (Stevenson and Hoyt, 1963).

The anatomical involvement of the brain-stem is not different in primary or secondary intraxial tumours, and a comparison of the neurological findings of our cases with the account of White (1963) on brain-stem glioma in adults predictably fails to reveal one unassailable criterion for their distinction from each other. Arteriography and pneumoencephalography in two cases in this series, showing a single lesion, were unable to distinguish between a primary
and secondary mass, so that the radiographic diagnosis in both was primary brain-stem glioma. A positive brain scan also cannot differentiate between glioma and metastasis.

The differentiation of a metastatic malignancy from a glioma comes to rest on recognition of a primary source or of other lesions elsewhere in intracranial or extracranial sites. Attention to results suggesting multiple lesions provided by EEG and brain scan (case 1), or bone films and blood chemical tests (case 2), is required. Continuing surveillance is necessary as later evidence for a primary tumour appears (case 3). The ancillary distinction of primary glioma from metastasis can be sketchy. In one series (Barnett and Millac, 1966) this reduced itself as to whether the chest film was positive, whether a single lesion rather than multiple lesions was shown on arteriography, and whether the erythrocyte sedimentation rate was raised. Unfortunately, the sedimentation rate may be normal with cerebral metastasis and significantly raised with a primary glioma (Hass and Harter, 1957) and metastases below a certain size are not revealed by arteriography or brain scanning.

Although survival with brain-stem metastases should logically be short, a swift course is not a reliable criterion. Certain gliomas may show a remarkably indolent course, and relapses and remissions have been pointed out with brain-stem gliomatata (Sarkari and Bickerstaff, 1969), but the overall spectrum of survival recorded by White (1963) is quite comparable with the present metastatic series. These tumours all centred on the pons, where tegmental involvement is not life-threatening and where full enlargement of the fourth ventricle provides maximum opportunity to avoid hydraulic blockade. The palliative role of whole brain radiotherapy of cerebral metastases is reported (Deeley and Edwards, 1968; Order et al., 1968; Hindo et al., 1970), but these do not identify location and the benefit for stem metastasis is moot. The addition of corticosteroid therapy has aided in producing good results (Hindo et al., 1970) as is to be expected from the presence of secondary oedema. Oedema complicates intrinsic and secondary tumours alike and remissions may be anticipated spontaneously, or under steroid administration with either. While this may affect quality of survival it is not clear whether duration is increased.

Furthermore, there is reasonable suggestion that corticosteroid therapy may actually promote the deposition or growth of somatic metastases (Sherlock and Hartmann, 1962).

The outlook for primary or metastatic brain-stem tumour seems related more to the biology of the individual neoplasm than to any broad difference in the behaviour between the two classes or the effect of therapeutic measures. The first case in this report, with very short survival, was an example of undifferentiated carcinoma of the lung. This contrasted with the somewhat longer survival of the second case, a fairly well differentiated adenocarcinoma of the lung. In a metastasis to the pons from carcinoma of the lung there was a 20 month survival (Hunter and Newcastle, 1968) and on steroid therapy there was even a regression of deficit before later recurrence. Our third case, a differentiated carcinoma of the kidney, is a neoplasm known to incorporate indolent behaviour of its metastases, which can regress after ablation of the source (Goodwin, 1968). Survivals with deposits unprecedented in other tumours are documented in renal cell carcinoma, and even cure after removal of a cerebral hemisphere metastasis (Lapin et al., 1965) is recorded. A metastasis to the cerebral peduncle from carcinoma of the kidney had shown deficit for at least three years before death (Hunter and Newcastle, 1968) without therapy. It would seem that some metastases adapt into stable parasites, in which cell turnover is exactly balanced between growth and death for prolonged periods of time.

We wish to acknowledge the helpful assistance provided by Mrs Marion W. Jones and Miss Sheridan Jackson.

REFERENCES

Spectrum of symptomatic brain-stem metastasis


