lieno-renal shunt has stopped further attacks of haematemesis and has led to considerable regression of the oesophageal varices.

At operation in Case 4, it was found that the splenic vein was embedded in a pancreatic mass, which was subsequently proved by histological examination of a biopsy specimen to be due to chronic inflammation. The large tortuous collaterals seen in the venogram actually belonged to the gastro-epiploic system of veins and obviously accounted for the bleeding.

Summary

Four cases of extrahepatic obstruction of the portal system of veins with repeated severe haematemesis and melaena are described. Two were due to cavernomatous transformation of the portal vein and two to obstruction of the splenic vein by chronic inflammatory pancreatic masses.

In three cases splenoportal venography clearly demonstrated the sites of obstruction and their possible nature. Both these findings were subsequently confirmed.

In addition to the routine methods of investigation, the advantages of splenoportal venography in such cases, both in diagnosing the cause of haematemesis and in planning the operation, are commented upon.

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CARCINOMATOSIS OF THE MENINGES

SOME CLINICAL AND PATHOLOGICAL ASPECTS

BY

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Diffuse carcinomatous spread in the meninges was first described by Saenger in 1900, although the neurological features seen in the terminal stages of malignant cachexia had been observed previously by Oppenheim (1888). Since the early German papers there have been many publications on this subject, and Jacobs and Richland (1951) were able to collect 52 cases. Fischer-Williams, Bosanquet, and Daniel (1955) have recently reviewed the condition.

It is probable that carcinomatosis of the meninges is commoner than the literature would lead one to suppose, for there is often no naked-eye abnormality, and unless histological sections are examined the diagnosis is not made. Furthermore, among Jacobs and Richland's cases there were no fewer than ten in which no primary neoplasm was found, and some cases may be missed altogether at necropsy and death be attributed to bronchopneumonia or other cause.

We describe two cases of carcinomatosis of the meninges which demonstrate different aspects of the disease and the possibility of improvement with treatment. The long survival of one—three years from the onset of symptoms—is unique.

Case 1

A labourer aged 68 was admitted to hospital on November 9, 1954, complaining of blindness. Four months previously he felt generally unwell, lacked energy, and had some pain in the neck. He later developed severe attacks of occipital headache, followed by anorexia and constipation. Two weeks before admission he found that his vision was deteriorating and his relatives noticed that he was groping about. On the day of admission he admitted that he was totally blind and had partly lost his hearing. In the past he had suffered from no serious illness apart from a paralysis of the left leg from infancy.

On examination he was confused, with marked neck stiffness and positive Kernig's sign, but afebrile. There was complete anosmia. Both eyes showed no perception to light, but the optic fundi were normal. The pupils were small and irregular, and did not react to light, though they reacted to attempted convergence. A rotary nystagmus was present with weakness of both external rectus muscles and partial dissociation of conjugate ocular gaze. There was slight right facial weakness of central type with partial bilateral deafness. No other abnormal neurological signs were found apart from the old flaccid left foot-drop. General examination showed mild hypertension (blood pressure 150/90 mm. Hg), the lungs and abdomen showed nothing abnormal, but the prostate was slightly enlarged.

The haemoglobin was 14.5 g. per 100 ml., the white cells 1,800 per c.mm., and the sedimentation rate (Westergren) 5 mm. in one hour. X-ray examination of the skull and chest showed no abnormality. Lumbar puncture gave a clear fluid under 300 mm. pressure, containing 28 lymphocytes per c.mm., with clumps of large mononuclear cells. In a Leishman film these had the characters of malignant cells. The fluid also contained protein 160 mg. per 100 ml., chlorides 700 mg. NaCl per 100 ml., and sugar 70 mg. per 100 ml.; the Wassermann reaction was negative. A left carotid angiogram showed separation of the vessels, suggesting internal hydrocephalus. A ventriculogram revealed dilated lateral and third ventricles, the fourth ventricle being normal. An electroencephalogram was not helpful.

The patient remained blind, with severe frontal and occipital headaches, but was still mentally alert until three days before death. He then became very drowsy and died on December 3, 1954.

Necropsy Findings

There was a primary diffuse infiltrating carcinoma of the stomach affecting all layers of the gastric wall, extending from the cardia to the pylorus and involving the lymph nodes of the lesser curvature. No other visceral metastases were found.

The brain showed a fine fibrinous exudate over the base, especially around the optic chiasma, and milky-white thickening of the arachnoid extended all along the spinal cord. The brain after fixation showed no visible metastases. The lateral and third ventricles were dilated, but the fourth ventricle was normal in size.

Histology.—The gastric tumour was a mucus-secreting, poorly differentiated carcinoma composed of sheets of "signet-ring" cells and clumps of small irregular acini. Sections of the base of the brain, including the optic chiasma and hypothalamus, of the cerebral and cerebellar cortices, and of the mid-brain, pons, and medulla showed a fine deposit of "signet-ring" carcinoma cells with a little fibrinous exudate scattered diffusely in the pia-arachnoid. Over the cerebrum the deposits were greatest between the convolutions. Similar tumour tissue was present in the arachnoid of the spinal cord and extended in the perineural

sheaths along the anterior and posterior nerve roots. Neoplastic cells were also present in the sheath of the optic nerve. There was loss of nerve cells in the superficial parts of the cerebrum close to the carcinomatous deposits, and degenerative changes were present in the optic nerve. The deposits extended to the perivascular spaces and were present within the aqueduct, which, however, was not completely occluded. No metastases were found within the cerebral substance.

Case 2

A carpenter aged 49 was admitted to hospital on May 18, 1948, having previously had no serious illness. Nine months before admission he developed pain in the distribution of the left sciatic nerve which was aggravated by bending and jolting. This was followed by paraesthesiae in the outer side of the left foot and some pain in the front of the right thigh. He was treated as a case of prolapsed intervertebral disk with physiotherapy and bed rest, and became pain-free.

Three weeks before admission he developed severe occipital headaches with vomiting. Double vision was followed by rapid deterioration of his vision, and on admission he was blind. His sciatica also recurred and was followed by weakness of the legs, retention of urine, faecal incontinence, and peri-anal numbness; the left arm also became weak.

On admission he looked ill but was afebrile. Nothing abnormal was found in the heart, lungs, or abdomen; blood pressure 180/110 mm. Hg. There was moderate neck stiffness and pain on straight-leg raising on both sides. The fundi showed severe bilateral papilloedema with haemorrhages and exudates. The visual fields showed severe peripheral constriction. Apart from horizontal nystagmus, the other cranial nerves were normal. The other neurological findings were somewhat confusing, but suggested a cervical cord lesion together with extensive involvement of the lumbar roots with spastic weakness of the arms, flaccid paralysis of the legs, and peri-anal anaesthesia.

The haemoglobin was 14.5 g. per 100 ml.; white cells, 11,300 per c.mm.; sedimentation rate (Westergren), 5 mm. in the first hour. X-ray examination of the chest and spine showed nothing abnormal. Lumbar puncture yielded a xanthochromic fluid at a pressure of over 300 mm. containing a few degenerate leucocytes; no malignant cells were seen. The protein was 2,800 mg. per 100 ml. Ventriculography showed normal symmetrical filling of the ventricles; the ventricular fluid contained only 50 mg. of protein.

During his first fortnight in hospital he became steadily worse, with mental confusion, severe headache, and vomiting.

A course of deep x-ray therapy to the whole of the brain and spinal cord was given between April 25 and July 5, the total dose being 4,000 r (250 kV). Improvement began almost at once, and after a week his headache was less severe and the vomiting had ceased. During the ensuing weeks he became completely free from headache, and by the end of the treatment he could walk the length of the ward without assistance. His visual acuity had returned to normal, although the disks developed optic atrophy. The only other residual signs were slight right facial weakness, nystagmus, and a partial left foot-drop with absent ankle-jerks. Lumbar puncture yielded a normal fluid at a pressure of 210 mm., and 40 mg. of protein per 100 ml. He was discharged from hospital and returned to work in December, 1948, having gained 30 lb. (13.6 kg.) in weight.

In March, 1949, the sciatic pain returned on the right side with limitation of straight-leg raising, diminution of the right knee-jerk, and pain on flexion of the lumbar spine. The C.S.F. protein was 200 mg. A second course of deep x-ray therapy was given (2,000 r) and the pain disappeared within a week, the C.S.F. protein again returning to normal.

He remained at work until December, 1949, when the right-sided sciatica returned, straight-leg raising was again limited, and the right knee- and ankle-jerks were diminished. He was readmitted on January 21, 1950, and the lumbo-

sacral roots were irradiated with 4,000 r with complete relief. He again remained well until April, when he developed pain in the neck aggravated by movement. Sensory loss appeared and was followed by dysuria, constipation, and impotence, and he was readmitted on May 24 with signs of a high cervical lesion. The C.S.F. protein was again 210 mg., but no malignant cells were found. A fourth course of deep x-ray therapy was given (4,000 r) to the cervical and thoracic cord, again with relief of pain and improvement in the physical signs.

He remained well for only a few weeks. In August he developed severe dysphasia, his headaches recurred, and he became mentally confused. He was readmitted on August 29 showing a complete paralysis of the left trigeminal nerve with dysphasia and a right hemiplegia, and died on September 8, 1950, without further treatment.

Necropsy Findings

Both lungs were congested and showed no tumour on routine serial slicing. Examination of the stomach, pancreas, intestine, thyroid, and adrenals showed no evidence of a primary tumour or of metastases. The prostate showed benign hyperplasia.

The leptomeninges over most of the parietal and temporal lobes of the left cerebral hemisphere were infiltrated by a layer of greyish-white tissue covering the brain with a thick plaque and obscuring the outlines of the convolutions. Similar whitish infiltration was irregularly distributed over the rest of the brain and the spinal cord. It extended to the spinal nerve roots, and the posterior root ganglia were greatly enlarged. Serial slicing of the brain revealed numerous discrete nodules, measuring up to 2 cm. in diameter, scattered through the cerebral hemispheres and in the superficial parts of the mid-brain and cerebellum. The ventricles were normal in size, and no tumour was found in the choroid plexus.

Histology.—Sections of all parts of the brain and spinal cord showed infiltration of the leptomeninges by undifferentiated tumour composed of closely packed small dark cells. Their nuclei were small, mostly vesicular in pattern, with clear nucleoli and scattered chromatin fragments. Other cells had darkly staining or hyperchromatic nuclei, and moderate numbers of mitoses were present. The cytoplasm was scanty, poorly staining, and ill-defined, the tumour cells being closely packed in irregular sheets and clumps. In some areas there was a linear grouping of the cells with occasional parallel arrangement of the line suggesting a poorly formed glandular pattern. In addition a few irregular glandular acini were found. True rosette formation was absent.

A well-formed reticulin network enclosed clumps of cells, but there was neither formed collagenous stroma nor closely intercellular reticulin. The thick layer covering the left temporal region was composed entirely of this tissue, which extended into the perivascular spaces of the brain. Similar tissue formed the discrete nodules, noticed macroscopically, and infiltrated the perineural spaces of the spinal nerves with extension into the root ganglia. Around the cord there were post-irradiation changes of fibroblastic thickening of the arachnoid with a little remaining tumour.

Comment on the Cases

In the first case the diagnosis of carcinomatosis of the meninges was made clinically, and was confirmed by the finding of malignant cells in the cerebrospinal fluid. The age of the patient, the site of primary growth in the stomach, and the rapidly fatal outcome are all typical of this condition. The illness was characterized by increasingly severe headaches, meningism, raised intracranial pressure, and blindness; in spite of both the latter features the optic fundi remained normal. Although on macroscopic examination the meninges were only slightly more opaque than normal, the microscopical appearances were typical, and foci of malignant cells similar to those of the gastric neoplasm were present in the aqueduct of Sylvius and round

the optic chiasma, explaining the internal hydrocephalus and the blindness respectively. This case resembled several previously reported (Walshe, 1923), although the number of occasions on which the diagnosis has been made in life appears to be small.

In the second case the most remarkable feature was the long duration of the illness and the long periods of freedom from symptoms. This was due to the deep x-ray therapy, and the outcome would undoubtedly have been as rapidly fatal as in Case 1 had it not been given. The onset with sciatic pain was initially confusing, since the pain improved with bed rest. He then developed severe headaches, with papilloedema, blindness, and evidence of severe cauda equina involvement. Ventriculography showed no evidence of a large intracranial mass, and it was thought likely that there was widespread dissemination in the subarachnoid space from either a primary spinal or a brain tumour. O'Connell (1946) described three cases in which a spinal neoplasm spread in this manner, and the form of onset in our patient suggested such a lesion. After irradiation improvement was spectacular. It is probable that the blindness was not due to the papilloedema but to direct invasion of the optic-nerve sheaths. His vision recovered at the same time as the other symptoms. Recurrences were similarly treated over a period of two years—the return of sciatica in the opposite leg seemed to confirm that the primary site of growth was in the lumbar region—and his pain was again completely relieved by irradiation, although the periods of remission became shorter.

The terminal state suggested a lesion in the left temporal lobe, and involvement of the left trigeminal nerve indicated that this lobe was invaded from without. He died three years after the onset of symptoms; during life there was no evidence of a neoplasm outside the central nervous system. The cellular pattern of the tumour in clumps and poorly formed glandular spaces, with the absence of intercellular reticulin, was interpreted as being that of undifferentiated secondary carcinoma. The histological alternatives of medulloblastoma, retinoblastoma, and neuroblastoma were regarded as unlikely in a patient of this age. No primary lesion of any of these types was found and rosettes were not present in the sections. The remaining possible histological diagnosis of diffuse undifferentiated sarcoma of the meninges was rejected on the grouped arrangement of the tumour cells within the reticular network.

Although no primary tumour was found, bronchogenic carcinoma was thought to be the most likely source of metastases, and the histological appearance of the growth supported this. Although this patient showed small rounded haematogenous metastases in the brain, these could not have been present for the whole duration of the illness, and they remained clinically silent.

Clinical Features

Although a few cases present as subacute or chronic meningitis, resembling tuberculous meningitis, most cases of carcinomatosis of the meninges show varying mixtures of cranial- and spinal-nerve involvement, often with blindness. Some resemble a rapidly expanding intracranial tumour, without localizing signs, and, rarely, a presenile dementia with fits. The absence of fever in a subacute meningitis is a strong indication that the case is one of carcinomatosis. Final proof of the diagnosis may be obtained by demonstrating malignant cells, although they are not always present. Special staining methods are not necessary for this—Leishman's stain, haematoxylin and eosin, and Papanicolaou's methods all being suitable (Spriggs, 1954). The very high C.S.F. protein in Case 2 has been seen in other cases. The presence of papilloedema may seem to contraindicate lumbar puncture, but if this condition is suspected the need for a substantive diagnosis would appear to override the risk.

Blindness of sudden onset in later life is a particularly important symptom, and the commonest cause is temporal

arteritis with bilateral thrombosis of the central retinal artery. Some cases of this show meningeal signs and headaches are invariably present, but differentiation is usually easy. In vascular lesions of the brain causing bilateral occipital lobe infarction the pupils will usually still react to light and denial of the blindness with confabulation is not infrequent. Retrobulbar neuritis is extremely rare in this age group, and, if these vascular conditions can be excluded, carcinomatosis of the meninges should be considered.

Pathological Aspects

In both cases tumour cells were present around the nerve roots, but secondary degenerative changes were not found, either in the spinal nerves or in the cord. Although the posterior nerve roots in Case 2 had been infiltrated for more than three years, no degenerative changes were present in the spinal nerves and cord at necropsy. Smith and Whitfield (1955) have recently suggested that carcinomatous neuropathy is due to direct invasion of the posterior root ganglia by tumour cells. In view of the length of history of this case, it is surprising that neuropathy had not occurred, and this is somewhat against their theory.

The possible sites of a primary tumour outside the nervous system are many, but Jacobs and Richland (1951) found that most were of gastric origin, and many of the rest were bronchogenic. Other sites have been found, however, and include pancreas, skin, and thymus, and it seems that any carcinoma may occasionally spread in this manner.

Several modes of spread from the primary site to the meninges have been postulated. According to Willis (1952, 1953) the most frequent route is from a small metastasis near the surface of the brain or from the choroid plexus with diffusion into the ventricles. Another route suggested is the invasion of peripheral nerve lymphatics by tumour and penetration of the meninges through the perineural arachnoid extensions. An additional route allows metastasis via the vertebral and epidural veins.

In Case 1 the extent of invasion of the aqueduct suggests that an initial intraventricular spread was more likely than one along the surface of the brain or cord. This juxtaventricular focus could have been a small ependymal or choroid plexus deposit. As sciatica was the first symptom in Case 2 it is possible that malignant infiltration began in the sacral nerve roots and spread to the leptomeninges along the perineural lymphatics. The enlargement of the spinal root ganglia in this region and their infiltration by tumour may indicate this first site of penetration of metastases into the nervous system. Histological evidence of infiltration of the distal points of the nerves is lacking, however.

Summary

Two cases of carcinomatosis of the meninges are described.

Deep x-ray therapy may produce a remission of symptoms and prolong life.

The diagnosis may be completely missed at necropsy unless material is sectioned for histological examination.

The possible mechanisms of spread of the disease are discussed.

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