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Meningeal Carcinomatosis

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ABSTRACT

Meningeal carcinomatosis without gross tumour in the substance of the brain or spinal cord has been reported rarely. Two cases observed at the Victoria General Hospital, Halifax, presented a bizarre clinical picture consisting of signs of meningeal irritation without fever, and psychotic behaviour. Examination of the cerebrospinal fluid revealed low sugar concentration and increased pressure, protein and cells. In one case these cells were readily identified as malignant on stained smears. At autopsy the surfaces of the cerebral hemispheres, cerebellum and brain stem were covered by an opalescent film and on section the subarachnoid space was densely packed with malignant cells. Both primary tumours were adenocarcinomas, one originating in the gallbladder and one in the rectum. The diagnosis of meningeal carcinomatosis must be considered in patients presenting with profound mental changes and meningeal irritation without fever. Diagnosis may be confirmed by cytological examination of the cerebrospinal fluid. The primary tumour is most commonly an adenocarcinoma. There is no satisfactory treatment available.

ALTHOUGH metastatic involvement of the central nervous system is not unusual in patients with carcinoma, occurring in 2% to 6% of most reported series, infiltration of the meninges without macroscopic tumour in the brain or spinal cord is relatively rare. Dixon, Kerr and Sharp[1] were able to find only 44 cases in the literature and Jacobs and Richland[2] only 52 cases.

In 1870 Eberth[3] described a case of tumour of the lung with tumour in the meninges, but he failed to associate the two. In the late 1800's it was commonly believed that visceral carcinomas elaborated a toxin which produced cerebral symptoms. The correlation of infiltration in the meninges with a primary malignancy outside the central nervous system was first made in 1900 by Saenger.[4]

As case reports of secondary meningeal infiltration associated with primary tumours outside the central nervous system appeared in the literature, there emerged a fairly distinct clinical entity with a characteristic pathological picture. It is the purpose of this report to present two cases of meningeal carcinomatosis seen recently at the Victoria General Hospital, Halifax, which illustrate many of the prominent features of the syndrome.

Case Reports

Case 1.—D.M., a 67-year-old white man, was admitted to Camp Hill Hospital, Halifax, on September 4, 1959. Five weeks earlier he began to have "blackout spells" which would occur up to five or six times daily. Two weeks prior to admission he developed confusion, headache and neck pain. A lumbar puncture was performed by his family physician shortly before admission. The pressure was not recorded but the protein content was 250 mg. % and the cell count 21 cells per c.mm., which were reported as "mostly lymphocytes". On the day of admission he was conscious but euphoric, confused and disoriented with visual hallucinations.

The physical examination showed evidence of considerable weight loss. Skull and chest roentgenograms were normal. Two days after admission, he gradually became comatose and the right pupil became fixed and dilated. Neck rigidity, a positive Kernig's sign, spasticity in all four limbs, bilateral extensor plantar responses and papilledema were noted. He was transferred the same day to the Neurosurgical Unit, Victoria General Hospital, Halifax, where slight improvement in the level of consciousness was noted after the intravenous administration of hypertonic glucose. A ventriculogram showed slight hydrocephalus but no evidence of a space-occupying lesion. Ventricular drainage was established, but his condition steadily de-

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teriorated and he expired 48 hours after transfer to the Victoria General Hospital.

Postmortem Findings

Autopsy revealed a tumour in the fundus of the gallbladder. This measured 3 cm. in diameter and was firm and slightly elevated, with rolled edges and a depressed, ulcerated centre. It involved the whole thickness of the gallbladder wall but did not invade the liver. Enlarged lymph nodes were present in the gastrohepatic ligament, in the parapancreatic region and retroperitoneally along the upper abdominal aorta. The nodes were firm, white and structureless and measured up to 2 cm. in diameter. The brain weighed 1400 g. and showed slight dilation of the lateral ventricles. Irregular, streak-like and patchy white areas were noted in the subarachnoid space, extending over the cerebral and cerebellar hemispheres, the pons and fourth ventricle. These consisted of finely granular material which had accumulated in the sulci, sparing the base of the brain. The cerebral vessels appeared normal.

Microscopic Examination

The gallbladder tumour was a poorly differentiated carcinoma composed of large signet-ring cells containing mucin. There was infiltration of all the layers of the wall. Widespread perineural and perivascular permeation was present in the serosa. Metastatic tumour cells were found in the adrenals, in the wall of the left atrium and in the aforementioned lymph nodes. The peribronchial nodes were extensively replaced by carcinoma. Carcinoma cells infiltrated diffusely the pia mater and arachnoid of the cerebral hemispheres, spinal cord and cerebellum, the outer layer of the cerebellar cortex and the roof of the fourth ventricle. The subarachnoid space was distended with tumour cells which extended into the perivascular spaces of Virchow-Robin. All the cranial nerves were surrounded by tumour cells and the spinal cord was ringed with a mass of tumour cells. Sections of the basal ganglia showed several large vessels that were surrounded by a cuff of tumour cells. There was no evidence of metastatic tumour in the substance of the brain or spinal cord, or in the choroid plexus.

CASE 2.—B.M., a 40-year-old housewife, was admitted to the Victoria General Hospital on November 8, 1961. On October 6, 1961, she had a difficult breech delivery of a healthy boy, her ninth child. The postpartum course was uneventful and she was discharged from hospital on October 10. Five days later she complained of headache, vomiting and backache. Examination by her family physician on November 1 revealed neck stiffness, and she was admitted to the local hospital where her temperature and pulse were noted to be normal. A lumbar puncture yielded slightly opaque spinal fluid with a pressure of 200 mm. There were 900 cells per c.mm., many of which were large and atypical. The protein content was 80 mg. % and the sugar content 12 mg. %. No organisms were seen on a stained smear and a culture was negative. Broad-spectrum antibiotics and sedatives were administered with slight improvement, but on November 7 deterioration with delirium and convulsions developed. A repeat lumbar puncture on this day showed a pressure of 450 mm. The spinal fluid again was slightly opaque and the cell count was 1500 per c.mm. She was transferred to the Victoria General Hospital on November 8 with a presumptive diagnosis of cryptococcal meningitis.

Examination revealed a moderately obese, extremely irritable woman who was disoriented, noisy and had hallucinations. There were marked neck rigidity and bilateral Kernig's signs. No abnormalities were noted on examination of the chest, heart and abdomen, or on pelvic and rectal examinations. The pupils were equal and reacted to light. There was slight blurring of the medial and superior disc margins but no venous engorgement. No cranial nerve abnormalities were noted, and there was good motor power in all limbs. The tendon reflexes were hypoactive and the plantar responses normal.

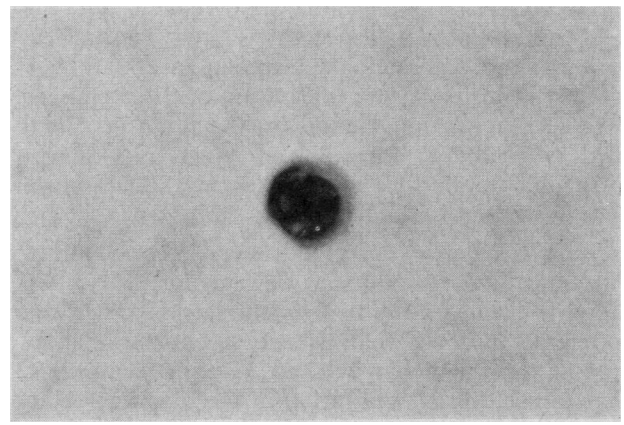

Fig. 1.—Papanicolaou preparation of cerebrospinal fluid (× 950). Large hyperchromatic cell showing coarse chromatin particles, prominent nucleoli and irregular nuclear membrane, approximately four times the size of normal lymphocyte.

The hemoglobin value was 16.6 g. %, the white blood cell count 13,350 per c.mm. with 84% neutrophils, and the erythrocyte sedimentation rate 22 mm. per hour (Westergren). The fasting blood sugar was 100 mg. % and the blood urea nitrogen and serum electrolytes were normal. A lumbar puncture on November 8 yielded a hazy fluid with a pressure of 600 mm. The cell count was 900 cells per c.mm., the vast majority of these being large mononuclear cells with a small amount of fibrillar blue cytoplasm and large nuclei containing dense chromatin and one or two nucleoli (Fig. 1). Many mitotic forms were present in these obviously malignant cells. The protein content was 52 mg. %, the sugar content was 17 mg. % and the chloride value was 115 mEq./l. No organisms were seen in a stained smear of the spinal fluid and cultures were sterile.

On the basis of the spinal fluid findings, 25 mg. of amethopterin was administered intrathecally on November 9. Twelve hours later, the spinal fluid pressure had fallen to 350 mm. and the cell count to 115 per c.mm. On November 11, the patient appeared to be blind. Neurological examination showed bilateral palatal weakness and gross bilateral papilledema. A low dose (100 r) of whole brain irradiation was administered but deterioration continued and she expired during the evening of November 11, 1961.

Postmortem Findings

A soft, fungating tumour with central ulceration and rolled edges was found on the posterior wall of the rectum just above the pectinate line. It encircled two-thirds of the rectal wall and measured 5 cm. in diameter. The surrounding mucosa was normal. No fixation or induration was present and there appeared to be little narrowing of the bowel lumen. Two firm white masses, each 2 cm. in diameter, were found in the right lobe of the liver. The para-aortic lymph nodes were enlarged to 2 cm. and were also firm and white. As this chain of nodes descended to the internal iliac vessels, the lymph nodes increased in size, the largest being in close proximity to the tumour.

The brain weighed 1320 g. A yellowish-white opalescent film covered the surface of the cerebral

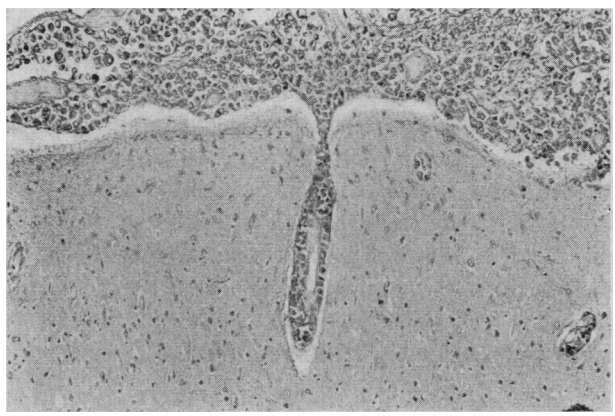

Fig. 2.—Cerebral cortex showing diffuse infiltration of subarachnoid space by undifferentiated tumour cells with infiltration of the Virchow-Robin spaces (× 100).

hemispheres, the cerebellum, the brain stem and spinal cord. This was thicker in some areas, particularly in the region of the sulci, around the vessels on the superior cerebral surfaces and about the base of the brain. Multiple sections failed to show any intracerebral tumour deposits and the choroid plexus was normal.

Microscopic Examination

Sections from the tumour in the rectum revealed a well-differentiated adenocarcinoma. In contrast to the primary tumour, the metastatic tumour in the lymph nodes and meninges was considerably less well differentiated, revealing marked cellular anaplasia and only occasional acinar differentiation. The pia mater and arachnoid were extensively infiltrated and the subarachnoid space was packed with malignant cells (Fig. 2). Many cells were of the signet-ring type, staining positive with PAS. The brain adjacent to the lateral ventricles and the choroid plexus was normal. The cranial nerves and the optic nerves in particular were completely encircled by malignant cells, which also extended into the perivascular spaces of Virchow-Robin, around the spinal cord and the spinal nerve roots.

DISCUSSION

In a review of 44 cases, Dixon, Kerr and Sharp[1] described three separate clinical forms of meningeal carcinomatosis. The first was characterized by slowly developing symptoms suggestive of a cerebral tumour, as noted in Case 1; the second, by involvement of the basal and spinal meninges that resembled polyneuritis; and the third, by a fulminating course resembling bacterial meningitis, as in Case 2. The cases reported by Heathfield and Williams[5] presented mainly with cranial and spinal nerve involvement, and these authors felt that only a few cases masquerade as cerebral tumour or meningitis.

In most reported series, signs of meningeal irritation have been very prominent. Signs of general ill health related to the primary tumour may be present but are usually overshadowed by the striking and often dramatic neurological manifestations. Headache is usually the first symptom and is followed by nausea, vomiting and signs of meningeal irritation. The absence of fever is noteworthy, being almost invariable in uncomplicated cases and of considerable importance in differential diagnosis. The "meningitic" form may resemble an inflammatory process and be confused with bacterial meningitis.

Meningeal carcinomatosis closely resembles meningeal leukemia. In both syndromes, there is a dense infiltrate of tumour cells in the subarachnoid space which blocks the flow and resorption of cerebrospinal fluid, leading to increased intracranial pressure with all its attendant symptoms and signs.

The frequent occurrence of loss of vision was emphasized by Fischer-Williams, Bosanquet and Daniel.[6] This was present in the three cases reported by these authors, and in nearly one-third of the cases they reviewed from the literature. The optic discs are often normal, but both atrophy and papilledema have been recorded. The patients described in this report demonstrated papilledema terminally and one patient (Case 2) appeared to be blind. A heavy cuff of tumour cells surrounded the optic nerves of both patients. In several reported series, cranial nerve palsies, especially oculomotor and facial, were early manifestations. The only cranial nerve sign in these two cases was bilateral palatal weakness in one. Both patients had multiple generalized seizures which have been reported infrequently elsewhere. Profound mental changes with disorientation and hallucinations, and signs of meningeal irritation were the most outstanding manifestations in the two cases reported herein.

Laboratory investigations are usually negative with the exception of studies of the cerebrospinal fluid.[7-9] The pressure and cell count are usually elevated, while an increase of protein content is less constant. The cerebrospinal fluid sugar content is often decreased and may be extremely low, as in Case 2, comparable to that seen in bacterial meningitis. The depression of the cerebrospinal fluid sugar that occurs in infections of the meninges with pyogenic, tuberculous and fungus organisms is well known, but may be overlooked as a sign of

neoplastic involvement. The mechanism whereby the spinal fluid sugar is lowered is poorly understood. Pleocytosis with the added accelerated metabolism of the neoplastic cells may be responsible. *In vitro* studies have demonstrated increased utilization of glucose by tumour cells.[10] In addition, alterations in the normal blood-brain barrier with mechanical blocking may affect the normal blood/CSF sugar ratio.

The most valuable and perhaps the most neglected procedure is cytological examination of the cells in the spinal fluid. The malignant cells are usually large—10 to 15 times the size of a lymphocyte—and may be readily recognized with appropriate staining. In Case 2, Romanowsky staining gave poor results for finer detail, but staining by Papanicolaou's method proved quite adequate and malignant cells were easily identified. Because of their extreme anaplasia, however, the course of the primary malignancy could not be ascertained.

Pathologically, the most common gross finding has been a hazy grey clouding or yellow streaking of the meninges which may be confined to the basal and spinal regions. In many instances nothing may be noted grossly, and unless sections are examined histologically, such cases may be missed. For this reason it may be that the incidence of meningeal carcinomatosis as given in the literature is falsely low.

Adenocarcinomas appear to have a greater affinity for the meninges than do other malignant tumours, and whereas gastrointestinal carcinomas rarely metastasize to cerebral substance, they not infrequently involve the meninges. In this regard, carcinoma of the stomach appeared to be the commonest primary tumour, followed by carcinoma of the lung.[1, 6, 7, 9]

Many of the primary lung tumours that gave rise to meningeal metastases were adenocarcinomas rather than anaplastic or squamous cell types. No cases were found in the literature of a primary tumour in the gallbladder or rectum, but there were several in which the primary tumour was in the large bowel. Other sites of origin included the pancreas, breast, colon and prostate. Several of the breast carcinomas metastasized to the meninges years after mastectomy. Heathfield and Williams[5] found a similar distribution and added cases of skin and thymus gland origin. Lesse and Netsky[11] found meningeal involvement more commonly with malignancies of the breast, lung and kidney. Jacobs and Richland[2] failed to demonstrate any primary tumour in 10 of the cases they reviewed.

The distribution of metastases to the central nervous system and the microscopic appearance were remarkably similar in the cases reported here. Dixon, Kerr and Sharp[1] remarked on the similarity of the histological picture, which appeared to be independent of the site or nature of the primary tumour in the 44 cases they reviewed.

The mechanism of spread from the primary neoplasm to the meninges is not known. In 1870 Key and Retzius considered that the tumour spread via lymphatics which communicate with the perineural spaces and in turn with the subarachnoid space. Further spread depended on mechanical factors such as gravity and the configuration of the subarachnoid space.

Invasion of the vertebral and epidural veins has also been proposed, but more recent reports favour direct invasion from the blood stream. In Case 2, one might postulate that the recent pregnancy and delivery which preceded the patient's death by only five weeks may have been an important factor in the dissemination of the tumour in the rectum through massage of tumour cells into the lymphatics and blood channels.

Treatment has been unsatisfactory. Several cases have been reported with a good response to whole brain irradiation, in which respect meningeal carcinoma resembles meningeal leukemia. Antimetabolites have been used infrequently and are of doubtful value. The use of intrathecal amethopterin in Case 2 failed to alter the course significantly. In keeping with the experience of others, both patients reported here had a rapid downhill course, neither surviving six weeks after the onset of symptoms.

SUMMARY

Two cases of meningeal carcinomatosis with clinical and pathological findings are presented. Both patients had symptoms and signs of meningeal irritation and an unusual neurological picture. In the second case, recognition of a low cerebrospinal fluid sugar content and malignant cells in the spinal fluid permitted a diagnosis to be made during life. The literature pertaining to this syndrome is briefly reviewed, and the characteristic histologic pattern with dense subarachnoid infiltration by malignant cells is described.

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