COMMUNICATIONS

A CASE OF SECONDARY CARCINOMATOUS INFILTRATION OF THE PIA-ARACHNOID OF THE BRAIN, PRESENTING EXCLUSIVELY OCULAR SYMPTOMS DURING LIFE: MENINGITIS CARCINOMATOSA

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I.—INTRODUCTORY

While the occurrence of secondary deposits in the brain in cases of visceral carcinoma is well recognized, yet when this secondary involvement takes the unusual form of a fine microscopic infiltration of the lepto-meninges, the clinical and pathological problems involved become of some interest. The clinical feature which has seemed to justify the recording of the present case was that during life the physical signs were exclusively ocular, whereas commonly this form of carcinomatous involvement of the central nervous system produces a clinical picture akin to that of an acute meningitis. Pathologically, though this is not unique in the condition under consideration, the case is of interest because the lesion was so fine as almost entirely to escape notice on naked eye examination of the brain. Indeed, its nature and extent were not revealed until microscopic investigation was undertaken.

As long ago as 1888, Oppenheim referred to certain cases of visceral carcinoma in which striking symptoms referable to the nervous system appeared in the terminal stages of the disease,
but in which examination of the nervous system, macroscopic and microscopic, revealed no lesion with which these symptoms could be correlated. He concluded that this part of the clinical picture was the result of a toxaemia of the nervous system due to toxic metabolites produced by the cancer cells and circulating in the blood.

Saenger\(^5\) took up the subject in 1901, and, as far as we are aware, was the first to describe the condition now under consideration. His cases bear a closer resemblance to the present than any others we have found in the literature. The first patient was a woman of 46, in whom after removal of the breast for carcinoma a local recurrence had occurred. She came under observation for headache and vomiting, diplopia and bilateral deafness. Examination revealed peripheral palsies of the right sixth and seventh nerves and bilateral nerve deafness. The fundi were normal. The knee jerks were sluggish, but no other signs referable to the nervous system were observed during life. At autopsy the brain presented scarcely any abnormality to the naked eye, but careful scrutiny revealed slight thickening and opacity of the pia-arachnoid along the lines of the vessels on the convexity of the hemispheres and at the points of emergence of the sixth, seventh, eighth and ninth nerves. Microscopically, this thickening proved to be due to an infiltration by carcinomatous cells. Saenger described a second similar case, in which, as in the new case here recorded, the nervous symptoms were unilateral blindness and abducens palsy. He refers to Oppenheim's earlier paper and rejects the hypothesis therein advanced, preferring to believe that Oppenheim was actually dealing with undiscovered carcinomatous infiltration of the lepto-meninges. In 1902, Siefert\(^7\) reported a small series of cases of the kind. He believed that owing to the vascular and embolic mode of spread of carcinoma the deposits in the brain tend to be superficial. When the lepto-meninges are involved, the malignant cells lie in the substance of the pia-arachnoid, spreading later from numerous foci into the subarachnoid space. A small round-celled infiltration may accompany the process, and may be so marked as to suggest the term "meningitis carcinomatosa." Siefert regarded the condition as clinically unrecognizable, but as one to be suspected when the clinical course of carcinoma is accompanied by rapid cachexia, apathy, dementia, delirium, symptoms suggestive of dementia paralytica, or of "hysteria."

In 1911, Schwarz and Bertels\(^6\) recorded a personally observed case of carcinomatosis and reviewed the literature of the subject, which was then and still remains almost exclusively German. The patient was a man in whom symptoms suggestive of gastric carcinoma were complicated by severe headache, accesses of mental excitement and a pulse rate of sixty and less. His condition is
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said to have resembled that seen in tuberculous meningitis, when he came under observation in the final stage of his illness. Lumbar puncture yielded a turbid fluid under increased pressure, the turbidity being due to the presence in great abundance of large epithelial cells. The naked-eye appearance of the brain presented no abnormality, but microscopic examination revealed that the subarachnoid space was packed with large cells of epithelial type including some giant multi-nucleated cells. The meninges themselves were normal, but the cells had penetrated into the perivascular spaces of arteries entering the brain and were found, exclusively in this situation, deep in the brain substance. They regarded the tumour from which these cells probably arose as a blastoma, but since a general autopsy was not obtained, the primary lesion was never seen.

From a general consideration of the cases we have quoted, and from that of those reviewed by Schwarz and Bertels, it appears that the usual clinical picture is one of acute meningitis, but the true nature of the condition present may be indicated by the occurrence in the cerebro-spinal fluid of cells of malignant type. Pathologically, the rule appears to be that tumour masses in the brain are absent from cases which show diffuse infiltration of the pia-arachnoid. We must remember, however, that a systematic examination of the meninges is seldom carried out in cases presenting carcinomata in the brain, and, as several authors suggest, "meningitis carcinomatosa" may be more common than is suspected. While such invasion of the nervous tissues as occurs is commonly exclusively perivascular, yet direct extension from the meninges is recorded. In these circumstances, the carcinoma cells destroy and replace normal nervous tissues in the affected regions.

A diffuse sarcomatosis of the pia-arachnoid, strictly comparable both in its clinical course and in the distribution of the lesion has also been recorded by Nonne(2).

II.—CLINICAL

Annie B., a married woman of 57, was admitted to University College Hospital on March 7, 1921, for progressive failure of vision in the left eye, diplopia and headache of six months' duration. For the whole of this period she had suffered from throbbing pains in the head, bitemporal and occipital in situation, and always most severe at night. Within a week or so of the onset of these symptoms she had begun to see double and to notice that the sight of the left eye was beginning to fail. For three months there had been a definite squint of the left eye, and for this period the left eye had been almost blind, so that double vision had ceased to be noticeable. For six weeks preceding
admission she had noticed occasional difficulty in swallowing solids. There had been neither nausea nor vomiting, but she had lost weight noticeably. Her past health had been uniformly good, she was the mother of four healthy children, had lost one in infancy and had miscarried once.

On examination she was seen to be a small, pale, thin woman. She complained of severe bitemporal headache and appeared in pain. Her mental and emotional state was normal. Speech was normal. In the right eye the visual field, acuity and the fundus were normal. In the left eye vision was reduced to perception of hand movements at twelve inches, but there was no manifest defect of the visual field. The temporal half of the disc was markedly pale. Auditory acuity was normal on both sides, and there was no tinnitus or vertigo. The pupils were equal, central and circular. The right reacted normally to light and to accommodation. The left reacted to accommodation and to consensual illumination, but not to direct light. There was a total palsy of the left external rectus, but no other defect of ocular movement. The remaining cranial nerves showed no abnormality. The motor and sensory systems were normal, and all reflexes normal and equal on the two sides. Examination of the skull revealed no local tenderness and the radiogram was normal. The cranial sinuses were normal. The Wassermann reaction in the blood was negative. No visceral lesions nor any signs of malignant disease were observed. There were no enlarged glands.

During the remaining six weeks of life no fresh localizing signs in the nervous system were observed, except for a slight paresis of the left half of the palate and occasional regurgitation of fluids through the nose. She complained of headache of increasing severity and frequency. She was seen by Sir Herbert Parsons ten days before death, and he reported as follows:—"The left disc is pale and its appearance suggests retrobulbar neuritis rather than tabetic atrophy. The visual field is normal for hand movements. The right disc is normal in appearance." During the last week of life the temperature began to rise and she became very restless and excitable, crying out continually and trying to get out of bed, so that morphia had to be given. The accesses of psycho-motor excitement alternated with periods of semi-coma. On auscultation moist sounds were audible all over the chest. Finally, she became cyanosed and died on April 17. Post-mortem examination revealed a healed tuberculous focus at the apex of the left lung and purulent broncho-pneumonia at both bases. There was old mitral stenosis of moderate degree. No signs of malignant disease were found in any part of the body. The base of the skull and the cranial sinuses were normal. The brain appeared normal on naked eye examination, but was some-
what red in colour and on the convexity of the left occipital lobe was a small area of old softening, apparently from an ordinary embolus. The vessels were comparatively healthy. Close examination of the left abducens nerve revealed that it was slightly thickened and opaque in appearance. The optic nerves, chiasma and tracts appeared normal. The pituitary was normal. Unfortunately, the cerebral hemispheres and the cerebellum were not preserved for microscopical investigation. There remained for this purpose the pituitary, the optic nerves, chiasma and tracts,

the mid-brain, pons, medulla and the first cervical segments of the cord. Almost the whole length of the left optic and abducens nerves was also preserved. On close scrutiny of the preserved portions of the nervous system after some weeks in ten per cent. formalin-saline solution it was seen that the pia-arachnoid covering the ventral surface of the pons and surrounding the cranial nerves at their points of emergence from the brain stem was somewhat thicker and more opaque than normal. This thickening which was barely perceptible to the naked eye was not quite uniform, but was most obvious along the line of the basilar artery and round the emerging fifth and sixth nerves, especially on the left.
On the medulla and on the dorsal surface of the mid-brain no abnormality was detected.

A large number of pieces of tissue from the optic nerves and chiasma, from the cranial nerves and from the brain stem were cut and stained by haemalum and eosin, haemalum and van Gieson, mucicarmine and Weigert’s elastic stain.

It was found that the pia-arachnoid in the regions of thickening, and also in places where no thickening was visible to macroscopic examination, was the seat of a malignant infiltration by a cubical-celled carcinoma. The superficial extent of this, as revealed by the study of a large series of sections, is indicated in Fig. 1. Here the lightly hatched areas indicate the seat of meningeal infiltration, while the deeply shaded areas indicate where, in addition, the nervous tissues themselves were invaded. The part of the brain shown in the diagram is that preserved for microscopic examination. Where the meningeal infiltration was thinnest the infiltrating cells were not invariably arranged on any definite plan, but lay in small scattered groups in the spaces of the pia-arachnoid, surrounded by a sparse small round-cell infiltration. Where the malignant cells were most abundant they were arranged into definite groups surrounding a central space and closely resembling the acini of a secreting gland. (Fig. 2.) The cells
were cubical or columnar in form, possessed an abundant finely granular cytoplasm, and contained mucin in many instances. The nuclei were large and of a coarsely reticular structure. Mr. T. W. P. Lawrence expressed the opinion that the condition was a secondary carcinomatous infiltration, the primary lesion being probably situated in the epithelium of the alimentary canal. Unfortunately no primary growth was found at autopsy. In several situations on the ventral surface of the pons, where small arteries were cut in longitudinal section at the point of penetration of the brain substance, a most interesting appearance was to be observed. Immediately surrounding the entering vessel was a sheath of tumour cells in acinous formation, but more deeply in the brain, and in advance of these was a well-marked perivascular infiltration by small lymphocytes (Fig. 3). For the most part invasion of the brain was perivascular, but in the midline of the pons there was also direct invasion by extension from

**Fig. 3.**

Oblique section through small artery entering ventral surface of pons, showing perivascular infiltration by carcinoma cells superficially, and by small lymphocytes more deeply. Groups of cells in acinous formation are seen in the pia-arachnoid covering the surface of the brain. 2/3rds in. objective, 4 eyepiece.
the meninges (Fig. 4). In addition to the infiltration of the pia-arachnoid covering the ventral and lateral aspects of the pons and medulla and surrounding the cranial nerves at their points of emergence there was a dense infiltration of the sheath of the left sixth nerve and an intense invasion of the nerve trunk itself. In the longitudinal section very few nerve fibres remained and the nerve trunk was a mass of large cubical cells lying in no definite arrangement. The left optic nerve was less intensely invaded than the sixth nerve, and was not surrounded in its whole periphery by infiltrated meninges (Fig. 5). Where meningeal infiltration was present, small lymphocytes occurred in abundance round each collection of malignant cells. Invasion of the nerve trunk was by way of the pial septa. Here and there, lying against these were small collections of tumour cells. The proximal part of the nerve was much more involved than the distal portion. In the latter case the meningeal infiltration was sparse and the invasion slight and confined to the peripheral areas of the nerve trunk. The chiasma and the optic tracts were not invaded. There was a single small patch of meningeal involvement on the left border of the chiasma and on its under surface.
The pituitary was normal in structure, but on the left side of the stalk was a small area of meningeal infiltration.

The fifth to the ninth cranial nerves on both sides, but more so on the left, were surrounded at their points of emergence and for two or three millimetres of their courses by a dense meningeal infiltration, the cells lying in closely packed acinous formation. The fifth was, in addition, locally invaded on both sides, though during life, repeated examination had given no clinical indication of this lesion.

The arteries lying on the ventral surface of the pons were surrounded by tumour cells, but their walls were everywhere intact, except that the adventitia of the basilar artery was infiltrated by small lymphocytes (Fig. 4). The walls of the veins, on the other hand, did not escape. In the case of a large vein lying beside the basilar artery, the whole wall down to the endothelium was densely invaded by large cubical cells and by small lymphocytes. No tumour cells were found lying in the lumen of the veins. On the medulla, the meningeal infiltration was
localized as indicated in Fig. 1. On the dorsal aspect of the mid-brain there was no infiltration of the meninges.

Summary: During the last six months of life the patient had suffered from a left abducens palsy and progressive primary optic atrophy with blindness of the left eye. Severe headache with no definite localizing characters accompanied these phenomena. Terminal symptoms were paresis of the left half of the palate and accesses of maniacal excitement. The broncho-pneumonia, which finally closed the clinical course of the malady, cannot be correlated with the intra-cranial condition, but its result was that the pathological study of the brain was made possible at a much earlier stage than would otherwise have been the case. Examination of the brain revealed a fine localized infiltration of the pia-arachnoid by cells of carcinomatous character, cubical and columnar in form and arranged in groups like the acini of a gland. The growth is regarded as a secondary deposit from a primary adeno-carcinoma, which was not found, but which was probably situated in the alimentary tract. The brain tissue on the ventral aspect of the pons was superficially invaded, in some parts by direct extension from the meninges, but also, and more markedly by a perivascular infiltration of entering arteries. In this situation, and deeper than the advancing cancer cells was a well-marked lymphocytic infiltration. The left optic and abducens nerves were invaded and surrounded by malignant cells.

Several points of interest, clinical and pathological, are raised by this case. The chronic course and the occurrence of isolated cranial nerve palsies appear to be unusual for the condition. The isolated occurrence of ocular symptoms from such a cause must be extremely rare, and is most closely approached by Saenger’s two cases. The diagnosis made during life was that of new growth at the base of the skull, and it is doubtful, even if lumbar puncture had been performed and had revealed the presence of tumour cells in the cerebro-spinal fluid, whether a more accurate one would have been possible. There was a conspicuous absence of any signs or symptoms indicating involvement of the meninges overlying the cerebral hemispheres, unless the terminal mental excitement be regarded as such. If we may judge by the literature, the clinical picture is commonly dominated from the commencement by cerebral symptoms, delirium, stupor, mental deterioration and Jacksonian fits. Unfortunately, in this case the cerebral meninges were not available for microscopic examination, and it would not be safe to assume that they were free from involvement.

On the pathological side the extreme fineness of the meningeal involvement and the fact that at autopsy it was entirely missed indicates the importance, a point on which all writers on the
subject are agreed, of a routine examination of the meninges in all cases in which visceral carcinoma has been complicated by the development of definite symptoms referable to the nervous system in its clinical course. It suggests, further, the danger of error which lies in the loose invoking of "toxaemia" as an explanation of disorders of nervous function for which no gross cause is readily apparent. The presence of a lymphocytic infiltration in association with the malignant one may indicate simply a meningeal reaction to the presence of foreign cells, or may in part be due to a noxious chemical activity of the latter cells.

REFERENCES


THE IMPORTANCE OF RADIOGRAPHY IN DOUBTFUL CASES OF OPTIC ATROPHY WITH SPECIAL REFERENCE TO PITUITARY DISEASE

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It is not improbable that many cases of pituitary disease, or disease in the neighbourhood of the pituitary fossa which eventually involves the hypophysis, are missed by ophthalmologists because the only obvious feature in the picture is optic atrophy. This ought not to be so, for it is to them that the majority of cases of hypophyseal involvement apply for relief. The features which tend to put the ophthalmologist off his guard are the frequency