Remote metastases from intracranial tumours

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SUMMARY A review of the primary tumours of the nervous system encountered over the past 16 years from the population of the west of Scotland uncovered only three tumours in which remote extracranial metastases had developed. In all three, there had been surgical intervention before the appearance of metastases. The findings in these patients are compared with those in other published accounts of this unusual complication.

Primary brain tumours probably account for less than 1% of all deaths, and the vast majority of these kill as a result of their intracranial effects, in contrast to most malignant tumours elsewhere in the body which are lethal largely as a result of metastases. However, it is now well recognised that primary intracranial tumours can give rise to extracranial metastases (Drachman *et al.*, 1963; Glasauer and Yuan, 1963; Eade and Urich, 1970; Karasick and Mullan, 1974; Russell and Rubinstein, 1977). All acceptable cases have been judged to be so by certain basic criteria, ie, a histologically proved characteristic tumour of the central nervous system, a sufficiently detailed necropsy to rule out the possibility of any other primary site, and similar histological appearances of the primary tumour and the metastases (Weiss, 1955). To date about 100 such tumours have been reported, the common factors in most cases being one or more neurological operations, irradiation, and a prolonged survival. Access of the tumour cells to the lymphatics or to veins outside the nervous system, mediated by surgical intervention, appears to be the principal means by which extracranial metastases become established. Paradoxically this is more likely to reach recognisable proportions now than in the past because of longer patient survival (Kepes *et al.*, 1976). Other modes of spread have also been recorded even less frequently, for example, to the pleura, peritoneum, and other sites, after the insertion of ventriculopleural, ventriculoperitoneal, and ventriculocaval shunts (Brust *et al.*, 1968; Wakamatsu *et al.*, 1971). Implicit in the development

of shunt metastases is antecedent dissemination in the cerebrospinal fluid.

In recent years it has also been recognised that remote metastasis may occur in the absence of any previous surgical procedure. As many as 10% of all cases of remote metastases reported have occurred in the absence of surgical intervention (Rubinstein, 1967; Anzil, 1970; Hulbanni and Goodman, 1976). Whether or not irradiation plays any role in promoting extracranial spread is equivocal, but it probably does not involve any additional risk. Much of the literature on remote metastatic spread of intracranial tumours is in neurosurgical journals, rather than in journals of pathology. This, together with the intriguing rarity of remote metastases, and the contemporary trend in oncology actively to search for and treat metastases at the time of primary diagnosis, led us to review the primary tumours of the nervous system encountered over a 16-year period in the Institute of Neurological Sciences, Glasgow, to determine the frequency of such spread.

Material and methods

The Institute provides a service for about three million people living in the west of Scotland, and in the period 1960-76 there were some 2750 astrocytomas, 600 meningiomas, and 100 medulloblastomas. During this period one example of each type of tumour developed extracranial metastases, as illustrated by the following case reports.

The biopsy and necropsy specimens were fixed in 10% buffered formal saline and embedded in paraffin wax, and sections were stained with haemalum and eosin, by van Gieson's method, by Laidlaw's reticulin impregnation technique, and with phosphotungstic acid haematoxylin for glial fibres.

Case reports

CASE 1

An 11-year-old boy was admitted to the Division of Neurosurgery in February 1958 with a one-month history of anorexia and vomiting. On examination there was papilloedema and nystagmus to the right. Ventriculography suggested a large mass to the right of the mid-line of the cerebellum. Posterior fossa craniectomy was carried out and complete removal was attempted. Histological examination showed a medulloblastoma and he was subsequently given a course of radiotherapy. The patient was readmitted in March 1960 with leg pain, when a myelogram showed a filling defect at the level of the fourth lumbar vertebra, consistent with metastatic spread, and further radiotherapy was given. X-ray examination in August 1960 revealed bony metastases, and a third course of radiotherapy was given. He died in November 1960, two years eight months after diagnosis.

Pathology

The tumour removed at operation appeared histologically as a highly cellular mass composed of darkly

Fig. 1 Case 1. Medulloblastoma in biopsy specimen of cerebellum. Highly cellular tumour composed of darkly staining cells with hyperchromatic nuclei. (Haemalum and eosin $\times 440$)

Fig. 2 Case 1. Medulloblastoma in lung. (H and E $\times 440$)

staining oval cells with ill-defined cytoplasmic outlines (Fig. 1). There was no distinguishing architectural arrangement. Mitotic figures were plentiful, and the stroma consisted of strands of collagen containing a variable number of thin-walled blood vessels. The appearances were typical of medulloblastoma.

At necropsy the calvaria contained numerous deposits of tumour. The dura was rather tense, and there were many large, flat plaques of firm, light grey extradural deposits of tumour. Separate nodules of similar tumour ($3.5 \times 3 \times 3$ cm) protruded from the posterior aspects of the cerebellar hemispheres. Large numbers of tumour deposits (up to 4 mm diam) were identified elsewhere in the body (for distribution see Table).

Histological examination showed residual medulloblastoma in the cerebellum, extending to involve the subarachnoid space locally. Again no rosettes were seen. Microscopically the metastatic deposits were similar to the primary growth (Fig. 2).

CASE 2

A 52-year-old woman was admitted to the Division of Neurosurgery in August 1958 with a 12-month history of staggering and unsteadiness of gait, increasing difficulty in speaking, and intermittent

Table Remote metastases from intracranial tumours

Patients	Age at death (yr)	Duration (diagnosis to death)	Location and diagnosis	No. of operations	Courses of radiotherapy	Sites of extracranial metastases
1	13	2 years 8 months	Right cerebellar medulloblastoma	1	2	Lungs, lymph nodes, vertebrae, ribs, testis, pancreas, liver
2	59	6 years 6 months	Right posterior fossa meningioma	2	0	Lungs, liver, kidneys
3	32	9 months	Right frontal giant cell glioblastoma	2	2	Lungs, lymph nodes, myocardium, liver, perirenal tissue, omentum

vomiting. On examination there was papilloedema, nystagmus, and ataxia of the limbs on the right. A firm swelling was present behind the right mastoid region. Posterior fossa craniectomy revealed a tough fibrous mass underlying the cervical muscles, invading the skull in the right occipital region, and extending extradurally into the posterior fossa. The tumour and invaded bone were subtotally removed. Histological examination showed a meningioma. The patient was subsequently given a course of radiotherapy and remained relatively well until January 1965, when she was readmitted for increasing ataxia, headaches, and mild dysarthria. On examination there was mild papilloedema and nystagmus. At operation there was a large mass of tumour extending through the occipital muscles and quite separate from the cerebellar tissue. Further excision was attempted, but the patient died four days after the operation, six years and six months after diagnosis.

Pathology

The tumour removed at the first operation was characterised by a rich vasculature consisting of endothelial channels surrounded by ovoid or fusiform cells with prominent vesicular nuclei and pale staining cytoplasm. The proliferating cells were disposed as whorls and showed a distinctive reticulin pattern that outlined the vessels and tended to envelop each cell or small group of cells (Figs 3 and 4). The appearances were those of the haemangiopericytic variant of angio-blastic meningioma.

At necropsy the principal finding in the brain was a mass of residual tumour ($4 \times 4 \times 3.5$ cm) in the right posterior cranial fossa, which had penetrated the tentorium cerebelli. Multiple metastatic nodules were present in the kidneys (Figs 5 and 6) and elsewhere (Table).

Histological examination showed a rather pleomorphic and partly necrotic tumour, similar in appearance to the surgically removed specimen. No tumour was found in the dural sinuses. The secondary deposits had histological features similar to those of the primary tumour (Fig. 6).

CASE 3

A 32-year-old woman was admitted to the Division of Neurology in December 1975 with a three-month history of progressive left frontal headache and blurring of vision. On examination there was papilloedema and clumsiness of the left hand. Investigations revealed a 6.0 cm mass in the right frontal region. Craniectomy was performed and a right frontal lobectomy was carried out. Histological examination showed a giant-cell glioblastoma.

Fig. 3 Case 2. Haemangiopericytic variant of angio-blastic meningioma in biopsy of posterior fossa mass. Vascular tumour consisting of endothelial elements surrounded by proliferating fusiform pale staining cells with vesicular nuclei. Note tendency to whorl formation. (H and E $\times 400$)

Fig. 4 Case 2. Same tumour as in Fig. 3. Note distinctive reticulin pattern. (Laidlaw's reticulin $\times 440$)

She was discharged home in January 1976 but was readmitted in April 1976 with intense headache, nausea, and photophobia. After further neurc-

radiological investigation craniectomy was performed and further tumour was removed. She was discharged in May 1976 for a course of radiotherapy. Over the next few months she remained well, but a mass of lymph nodes appeared in the right side of the neck, which began to cause considerable discomfort by August.

By late August 1976 her general condition had deteriorated with recurrence of the headaches and disturbed vision in the left eye. She died in September, nine months after initial presentation.

Pathology

The tumour removed at the first operation was made up of bizarre, irregular, and frequently multinucleated giant cells with coarse often blunt processes and large vesicular nuclei with conspicuous nucleoli (Fig. 7). Mitotic figures were moderately numerous, and reticulin fibres were disposed around thin-walled blood vessels. The occasional cell contained glial fibrils. No evidence of ganglionic differentiation was found and no pigment was identified. The appearances were those of the giant-cell variant of glioblastoma.

At necropsy there was a mass of lymph nodes in the right upper neck ($6 \times 5 \times 5$ cm) with an irregular, lobular outline, firm consistency, and greyish-white colour on sectioning (Fig. 8). There was no apparent continuity with the craniotomy site.

Numerous enlarged lymph nodes were also present in the anterior and posterior triangles of the neck, extending down into the mediastinum. Scattered

Fig. 5 Case 2. Multiple deposits of tumour in kidney.

Fig. 6 Case 2. Deposit of haemangiopericytic variant of angioblastic meningioma enveloping glomerulus. (H and E $\times 440$)

Fig. 7 Case 3. Giant-cell glioblastoma in biopsy of frontal lobe. Tumour consists of irregularly shaped and frequently multinucleated giant cells with large vesicular nuclei and conspicuous nucleoli. (H and E $\times 440$)

nodules of 1.0 cm diam tumour were found in the lungs and in the myocardium. Numerous other deposits (up to 1.0 cm diam) of tumour were also seen (Table). The main finding in the brain was a large surgical defect in the right frontal lobe with no gross evidence of residual tumour.

Histological examination showed residual pleomorphic giant-celled tumour at the site of operation, in the meninges and ventricles, and within the anterior tributaries of the superior sagittal sinus (Fig. 9). The microscopic appearances of the intra- and extra-cranial tumour were very similar, and

Fig. 8 Case 3. Deposits of glioblastoma in cervical lymph nodes.

Fig. 9 Case 3. Infiltration by glioblastoma of tributary of superior sagittal sinus. (H and E $\times 440$)

were considered to be those of a giant-cell glioblastoma (Fig. 10).

Discussion

Many hypotheses have been offered to explain the great rarity of extracranial metastases of primary intracranial tumours. The absence of cerebral lymphatics, immune reactions to tumour cells crossing the blood-brain barrier, and the short postoperative life span of these patients have all been regarded as significant factors (Smith *et al.*, 1969). The proclivity for metastatic spread after surgical intervention has also been emphasised (Rubinstein, 1967), even though there have been cases in which metastases have occurred without prior neurosurgery (Russell and Rubinstein, 1977).

All three patients in our records had at least one major neurosurgical operation before the clinical appearance of metastases, which in each case were not proved beyond doubt until after death. In case 3, venous infiltration was demonstrated histologically, although the sites of metastases, as also in case 1, indicated lymphatic spread in addition. Haematogenous spread, while contributory in these two patients, appeared to be exclusively

responsible, in the second case, for the extracranial metastases.

Extracranial metastases from gliomas (Glasauer and Yuan, 1963; Rubinstein, 1967; Brust *et al.*, 1968; Smith *et al.*, 1969; Anzil, 1970; Eade and Ulrich, 1970; Wakamatsu *et al.*, 1971; Hulbanni and Goodman, 1976; Kepes *et al.*, 1976; Russell and Rubinstein, 1977), medulloblastomas (Drachman *et al.*, 1963; Glasauer and Yuan, 1963; Smith *et al.*, 1969; Russell and Rubinstein, 1977), and meningiomas (Glasauer and Yuan, 1963; Shuangshoti *et al.*, 1970; Karasick and Mullan, 1974; Russell and Rubinstein, 1977) are well recognised. It appears that venous and/or lymphatic permeation, facilitated by craniotomy and a relatively long survival (Alvord, 1976), were the routes of dissemination in our cases. The boy of 13 (case 1) with the medulloblastoma survived 2 years eight months, but, in common with medulloblastomas in general, there were no unique histological features of prognostic value, even on retrospective examination. The 59-year-old woman (case 2) with the haemangiopericytic variant of an angioblastic meningioma survived six years six months, and this no doubt facilitated the development of distant metastases in a tumour recognised to have an aggressive nature

Fig. 10 Case 3. Deposit of glioblastoma in myocardium. (H and E $\times 440$)

with early recurrence. Approximately 15% of meningiomas that metastasise are said to have an angioblastic pattern (Shuangshoti *et al.*, 1970). Finally, the 32-year-old woman (case 3) with the glioblastoma survived nine months, this type of tumour forming the majority of gliomas with remote extracranial metastases (Smith *et al.*, 1969).

The incidence of metastasising primary intracranial tumours is not known, but Smith *et al.* (1969) found 35 cases in over 8000 tumours of neuroectodermal origin in the files of the Armed Forces Institute of Pathology. Of these, 23 were glioblastoma multiforme, eight were medulloblastoma, and four were of other types. In our experience, the incidence is considerably less, there being only two examples in some 2850 tumours of neuroectodermal origin, the apparent difference probably being due to material of particular interest being referred to the Armed Forces Institute of Pathology. Accordingly, while extracranial metastases of neuroectodermal tumours are rare, examples should occur within the experience of most departments of neuropathology.

The formation of metastases depends on the tendency of malignant tumour cells to detach from the primary site and implant themselves elsewhere.

The biological basis of invasion and metastasis is not understood, although differences in cell surface properties between malignant and normal cells are known which perhaps explains in part the ability of the former to metastasise. For example, malignant cells are less tightly adherent to one another, perhaps related to a diminished calcium content and high negative surface charge of malignant cells (Prehn and Prehn, 1975). In addition, some neoplasms produce substances such as hyaluronidase, which might facilitate invasion.

Each malignant neoplasm not only has a certain probability of metastasising, but also has certain sites of predilection, unfortunately not predictable in every patient. These sites are not determined by purely anatomical considerations, and the 'seeding' of metastases in favourable 'soils' is largely unexplained. It is commonplace clinically to see one patient with metastatic disease from a small or occult primary and another with a huge tumour of similar histological type which has not metastasised. This is due to complex factors, such as tumour growth rate, degree of differentiation, and the presence or absence of barriers to spread.

Another factor is the immunological status of the patient, and differences have been shown between cancer patients and normal individuals and between patients with and without metastases (Cochran *et al.*, 1976). Most studies of the role of immunological integrity have, however, been on animals for ethical reasons, and to obviate the uncontrollable variables of the human situation.

Haematogenous dissemination of cancer cells leads to the most far-reaching effects of malignant disease, the cells reaching the bloodstream either after lymphatic spread or by entering the (venous) circulation locally, often before clinical recognition of the tumour (Schabel, 1975). The mere presence of cancer cells in the blood is, however, no proof that distant metastases have been established. Cancer cells often enter the blood quite early on in the disease, but most of them are killed there, or fail to grow in organs to which they are carried (Moore *et al.*, 1957; Madden and Karpas, 1967; Hoover and Ketcham, 1974). Cell culture has suggested that variable adhesion of target organ cells to metastatic tumour cells may be implanted in this context (Nicolson and Winkelhake, 1975). Experimentally, tumour cell arrest in organs is influenced by host immune status but does not correlate with tumour survival or development into viable metastases (Fidler *et al.*, 1977). Recent experimental approaches have inhibited entrapment of circulating tumour cells by administration of anticoagulants, presumably by their effects on coagulation mechanisms, which the metastatic

tumour cells may activate and which may favour their entrapment and multiplication (Hoover and Ketcham, 1975).

The most clamant question posed by our findings concerns the reasons for the extreme infrequency of metastases from primary central nervous system tumours. In many cases these tumours may kill by raising intracranial pressure before metastases have developed. This is corroborated by studies in which intracerebral transplantation of tumours, such as melanomas known to metastasise, killed the recipient animals by raising intracranial pressure with no development of metastases (Greene and Harvey, 1964). If, however, various tissues from these animals were transplanted, metastases did eventually occur in the transplanted tissue, suggesting that there was no absolute barrier to development of metastasis from intracranially located tumours.

The human situation is not straightforward, however, because factors such as prolonged survival, treatment with steroids, vascular invasion, previous surgery, or radiotherapy to the tumour may be found in patients with tumours which have *not* metastasised. Although certain histological types are said to occur more frequently in primary central nervous system tumours that do metastasise, these are not *unique* morphological features and may also occur in non-metastasising tumours. The possibility of identifying metastasising tumours biochemically has recently been recognised (Allen *et al.*, 1977), and specific tumour-associated antigens or altered immune responses may also permit metastasis (Hitchcock *et al.*, 1977). These latter workers further claimed the presence of a dicentric chromosome marker in a long-surviving glioblastoma multiforme patient with metastases. A test which could predict the chances of distant metastases in central nervous system tumours in *individual patients* would be desirable.

Prediction of metastatic spread of malignant tumours by immunological or other means is still in its infancy, but, in melanomas, recent promising results have been obtained using serum-mediated leucocyte migration inhibition (Mackie *et al.*, in press). This type of approach would be of immense value in separating out those patients in whom the adverse effects of prophylactic adjuvant therapy, such as cytotoxic drugs, are more than counterbalanced by a real chance of tumour cell destruction.

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