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Cerebral Metastases in Childhood Malignancies

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Summary

Between January 1982 to June 1994, 154 children with non-CNS malignant tumours excluding leukaemias and lymphomas were admitted and treated at the UKMC. Symptomatic (10 cases; 6.5%) and non-symptomatic (2 cases; 1.2%) cranial metastases (calvarial, dural and/or parenchymal) were seen in 12 (7.8%) cases. Among these 12 cases, 7 had intracranial parenchymal metastases (4.5%). Three cases had multiple intracranial parenchymal metastases. Only one case had infratentorial (cerebellar) metastasis. The patients' ages ranged from 1 to 18 years (mean age was 7.3 years). The male : female ratio was 5 : 2. While six patients' brain metastases diagnosed during subsequent relapses, one patient first presented with brain metastasis. Time elapsed between the diagnosis of the primary disease and intracranial metastasis ranged from 0 to 755 days (mean 327 days). Histopathological diagnoses were confirmed in 4 cases who had craniotomy and tumour removal. Mean survival following the diagnosis of intracranial lesion was 157 days (ranged from 0 to 412 days). Despite the aggressive treatment, including surgery, chemotherapy and radiotherapy, 6 cases died with progression or relapse of the intracranial disease.

In conclusion, the incidence of paediatric intracranial parenchymal metastasis is 4.5%. Prognosis is poor and intracranial disease is the primary cause of death.

Introduction

Intracranial parenchymal metastasis is a well-known neurological complication of malignant disease in the adult population with up to 40% incidence, and the great majority of patients die within 1 year of diagnosis [19]. However, cerebral metastases from non-leukaemic and non-lymphomatous malignancies during childhood are rare. Advanced and effective chemotherapy results in prolongation of survival and even cure in common paediatric malignancies. Patients who live longer are likely to exhibit different patterns of disease recurrence and related systemic or neurological complications. These complications range in seriousness from relatively fatal to trivial. Among the neurological complications, brain metastasis has the most dismal prognosis, and requires combined treatment to extend the length of survival.

In order to determine the prognosis and the value of the combined therapy (surgery, radiotherapy and chemotherapy) of the seven children with parenchymal brain metastases, the authors reviewed the records of 154 children who had non-CNS, non-leukaemic and non-lymphomatous solid malignant tumours over the past 12 years.

Patients and Methods

Between January 1982 to June 1994, clinical records of 154 children with non-CNS malignancies were reviewed. Children with lymphomas and leukaemias were excluded from the study. Likewise, children with CNS involvement resulting from extension of primary tumours from contiguous parameningeal sites such as the middle ear, orbit and nasopharynx are not included. Twelve patients (7.8%) had cranial (calvarium, dura mater and/or CNS parenchym) metastases. Seven (4.5%) of them were diagnosed as having intracranial parenchymal metastases. The clinical, radiological, histopathological findings and anatomical location of the primary tumours of seven cases were outlined in Table 1.

Histopathological diagnoses of the primary disease of 7 cases follow: Wilms' tumour (WT) 2 cases; neuroblastoma (NB) 2 cases; malignant melanoma (MM) 1 case; hepatocellular carcinoma (HC) 1 case; and angiosarcoma (AS) 1 case. The ages ranged from 1 to 18 years. The male : female ratio was 5 : 2. All children had clinical symptoms, suggesting cerebral metastases. Time elapsed between the diagnoses of primary diseases and the intracranial disease ranged from 0 to 755 days (mean 327 days). Histopathological diagnoses of intracranial lesions were confirmed in 4 cases (cases 3, 4, 5, 7).

While six patients' brain metastases diagnosed during the subsequent relapses, one of the Wilms' tumour case presented initially with intracranial metastasis.

Two of these 7 cases had additional neurological complications. These are cis-platinum related bilateral hearing loss (VIII. nerve neuropathy) of the hepatocellular carcinoma patient (case 3) and metastatic spinal column involvement of the T10-T11 bodies of a WT patient (case 4).

Only two cases (cases 4, 7) had concurrent lung and brain metastases.

Results

All patients survived less than a year following the diagnosis of the intracranial disease. All deaths but one were due to progression of the intracranial disease. Only one NB case (case 2) survived 363 days following the diagnosis of intracranial metastasis. Since the family declined surgery, one year remission was obtained by chemotherapy (cytoxan, DTIC, VCN, Cis-platinum, adriamycin), radiotherapy, bone marrow transplantation, and monoclonal antibody therapy. This patient died with progression of the primary disease.

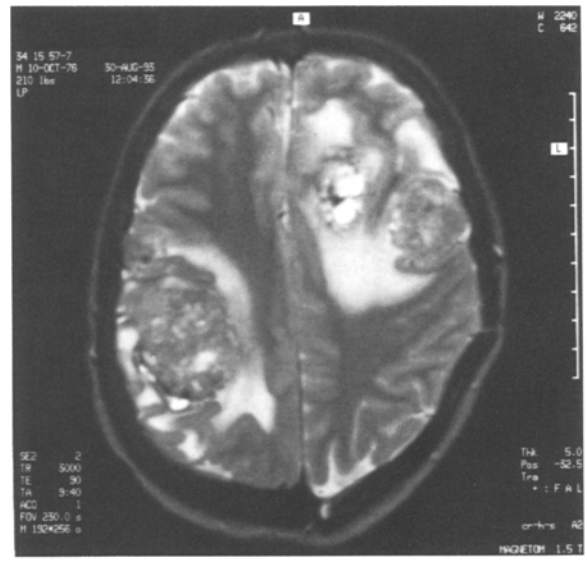
Three cases (cases 1, 6, 7) had multiple intracranial metastases.

The other NB case (case 1) had grand-mal seizures, and axial CT scan of brain showed multiple cerebral parenchymal lesions (possibly metastases). This patient died with status epilepticus on the same day of the diagnosis and the histopathological diagnosis of the intracranial lesions was not obtained.

One of the WT cases (case 6) had first relapse with calvarial and multiple bony metastases. Although remission was achieved with chemotherapy and radiotherapy during the first relapse, the second relapse was characterized by lung and intracranial parenchymal metastases. This patient died 32 days after the diagnosis of cerebral metastases.

The MM case (case 7) had three subsequent intracranial relapses. First relapse was characterized by a left parieto-occipital epidural mass, one year after the resection of axillary cutaneous MM. Following left parieto-occipital craniotomy, epidural tumour resection and cranioplasty, 9 months remission was achieved. Second relapse was characterized by multiple intracranial parenchymal metastases, along with a cerebellar metastasis (Fig. 1 a, b). Bilateral craniotomies and resection of 3 lesions along with gamma-knife radiosurgery for the cerebellar lesion were carried out. However, the patient died, 2 months after the third relapse.

Case 3 had hepatocellular carcinoma diagnosed by abdominal axial CT scan, and brain metastasis was found 72 days after diagnosis of the primary tumour. His axial CT scan and MR imaging of brain showed a right frontoparietal enhancing lesion (Fig. 2 a, b). The patient died 15 days after the right frontoparietal craniotomy and tumour removal. This patient had also chemotherapy (Cis-platinum) related bilateral hearing impairment (VIII. nerve neuropathy).



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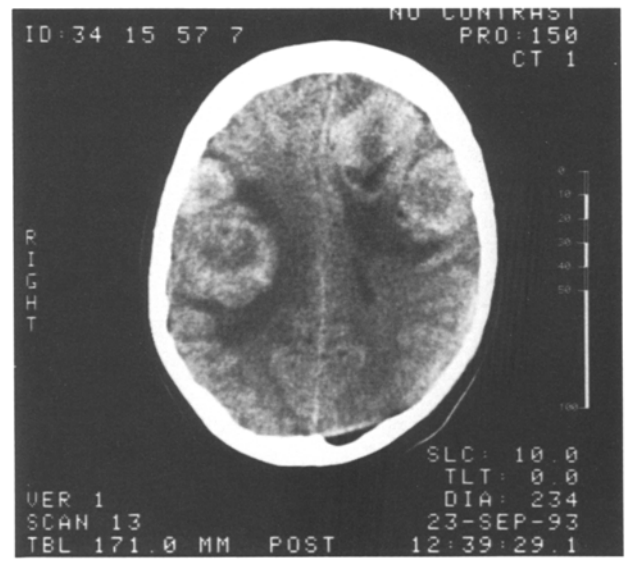

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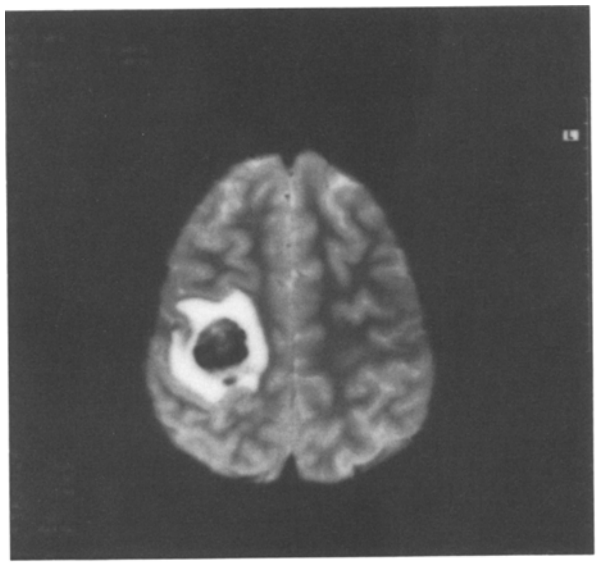
Fig. 1. (a, b) T-2 weighted axial MR image (a), and axial CT scan of the brain show multiple intracranial parenchymal metastases in the malignant melanoma case

Case 4 had Wilms' tumour of the left kidney. 47 days after diagnosis, a CT scan showed a left parietal intracerebral haematoma. The intracerebral haematoma was drained by left parietal craniotomy and the histopathological diagnosis of the haemorrhagic lesion was Wilms' tumour. He died 37 days after the diagnosis of brain metastasis. This patient had also spinal column metastases of the T10-T11 bodies.

Case 5 had angiosarcoma of the mandible. Twenty



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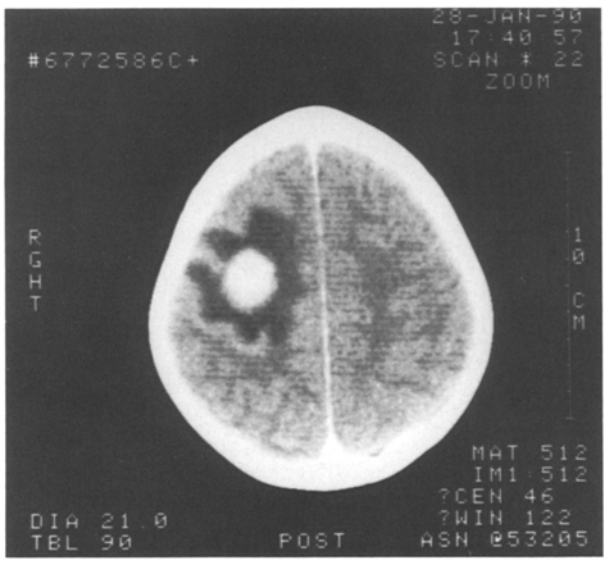

b

Fig. 2. (a, b) The T-2 weighted axial (a) MR and contrast enhanced axial CT scan (b) images of brain show the single metastatic lesion of the hepatocellular carcinoma in the right parietal area

days after the diagnosis of primary lesion, MR imaging of the brain showed an isolated parenchymal lesion in the left temporal lobe. Although the left temporal parenchymal lesion was totally resected, he died on the 20th postoperative day of craniotomy.

Discussion

Following retrospective review of the case histories, CT scan and MRI files of 154 children, the incidence of brain metastasis was found to be 4.5% in this series. The incidence of brain metastases in paediatric populations has been reported in three different series [6, 10, 27] as 2% (review of the CT scan and diagnostic test files), 6.1% (review of autopsy files) and 13% (review of autopsy records or computed tomography scan files). Jones and Campbell [11] reported only four cases (0.7%) of cerebral metastasis among 567 children with solid tumours seen at the Royal Children's Hospital Melbourne over a 23-year period. Moreover, Tomita *et al.* [25] reported only 4 paediatric metastatic brain tumours among the 403 paediatric brain tumours between 1967–1982.

The most common non-CNS non-lymphomatous and non-leukaemic childhood solid tumours are NB, rhabdomyosarcoma (RMS), ES, WT, and osteogenic sarcoma (OS) [26]. These solid tumours constitute 30% of childhood cancers [26]. Brain metastasis had been an uncommon neurological complication of childhood solid malignant tumours. However, this has been changed with prolonged patient survival in the modern chemotherapy era.

In our study, 32 (20.8%) of 154 cases had NB/GNB. Seven (21.9%) of these cases had cranial metastases and 2 (6.2%) cases had parenchymal brain metastases. Kellie *et al.* [12] found 10 (6.2%) CNS metastases among the 160 primary abdominal or thoracic NBs. Five (50%) of these cases showed also evidence of metastatic disease involving the bony orbits, calvarium or base of the skull. However, according to Reddemann *et al.* [20], the occurrence of intracranial disease by contiguous spread from disease of the dura or skull is not unusual, and most patients with NB, apart from orbital spread, are not considered to be at risk from intracranial disease; thus, their initial investigation does not normally include CT scanning of the head. However, one of our NB cases had retro-orbital involvement along with an isolated temporal parenchymal metastasis on the same side. Although intraparenchymal diseases may occur less frequently, it has been suggested that in NB presence of metastasis to the orbit and calvarium strongly correlates with the presence of CNS metastases [5, 23]. The incidence of parenchymal brain metastasis in NB has been reported between 1% to 6.2% in different series [5, 12, 21, 22]. Metastases from NB by cerebrospinal fluid pathways are extremely rare [7]. According to autopsy findings, Dresler [7] suggested that the tumour penetrated the spinal meninges and disseminated through the cerebrospinal fluid.

WT almost invariably arises from the renal cortex

Table 1. *Clinical, Diagnostic and Anatomical Findings in 7 Cases of the Brain Metastases* (+ indicates the occurrence of lung metastases at the time of diagnosis)

Case no.	Sex	Age at diagnosis	Location	Histopathological diagnosis	Interval between diagnosis & intracranial metastasis (days)	Lung metastasis at diagnosis	Therapy	Symptoms and signs	Other neurological complications	Methods of diagnosis	Outcome	Survival after intracranial diagnosis (days)
1	F	1	left surreal gland	neuroblastoma	185	–	CT	grand-mal seizures	–	CT scan	died	0
2	M	2	right surrenal gland	neuroblastoma	0	–	CT + XRT	partial left III.	–	CT scan	died	363
3	F	6	liver	hepatocellular carcinoma	72	–	surgery	left hemiparesis headache bilateral extensor plantar responses	CT related bilateral VIII. nerve neuropathy	CT scan MRI histopathology	died	15
4	M	3	left kidney	Wilms' tumour	42	+	CT+ surgery	headaches vomiting drowsiness	$T_{10\text{-}11}$ metastasis	CT scan histopathology	died	37
5	M	18	mandible	angiosarcoma	20	–	XRT + surgery	headaches vomiting drowsiness	–	CT scan MRI histopathology	died	30
6	M	6	left kidney	Wilms' tumour	755	–	XRT	seizures & drowsiness	–	CT scan	died	23
7	M	16	left axilla	malignant melanoma	645	+	XRT + surgery	left hemiparesis seizures ataxic gait	–	MRI histopathology	died	127

CT chemotherapy, *XRT* radiotherapy, *CT scan* computerized tomography scan, *MRI* magnetic resonance imaging.

and the most common tumour of the genito-urinary tract in children [3]. Cerebral metastases from WT may occur in the late stages of the disease. According to Takamiya *et al.* [24], intracranial metastases of WT are very rare and spontaneous intracranial haemorrhage of the metastatic WT is an unusual clinical presentation of brain metastasis. Moreover, among the 417 cases of WT, Akyuz *et al.* [1] found only 2 cases of brain metastasis. However, according to Vanucci *et al.* [27], WT is the most common histological type among the metastatic brain tumours in children, and the incidence was 12.9% in their study, and 1/3 of those cases had multiple brain metastases. In our series, among the 19 (12.3%) WT cases, only 2 (10.5%) of them had intracranial parenchymal metastases, and one case had multiple intracranial parenchymal metastases.

In our review, forty cases (26%) had sarcomas (OS, ES or soft tissue sarcomas). However, only one case (angiosarcoma) (2.5%) had parenchymal brain metastasis. None of the OS, ES and rhabdomyosarcoma cases had intracranial parenchymal metastasis, during their treatment and follow-up. Baram *et al.* [2] reported 5 cases of OS with brain metastases among the 87 paediatric OS patients. All patients with brain metastases had developed pulmonary disease, and some of which were resected. In all cases the appearance of brain metastases was concurrent with or subsequent to, occurrence of lung metastases. They could not find any predilection of particular age or pathological variant of OS for the development of brain metastasis. Clinical presentation of their cases were acute and catastrophic. All of those cases required emergency management and accompanied with major morbidity. They recommended routine periodic screening of the brain by CT or MRI for early detection of the metastatic lesions, to prevent the catastrophic complications of brain metastasis. The incidence of brain metastasis of soft tissue and osseous sarcomas has been reported at between 5% to 16% [2, 13–15].

Among the 154 cases, we encountered 6 cases with primary malignant liver tumours. Only one case had a solitary brain metastasis. However, among 48 infants and children with primary malignant liver tumours, Giancomantonio *et al.* [9] did not describe any brain metastasis, although seven of their patients had pulmonary metastases.

Two main theories of metastasis have been proposed. The "soil-seed" hypothesis was originally described by Paget [18] in 1889. According to Paget [18], the distribution of tumour metastases is explainable on the basis of favourable micro-environments in certain organs. However, the mechanical theory, which was proposed by Ewing [8], explains the distribution of tumour metastases entirely on the basis of blood flow patterns. The recognized primary risk factor of brain metastasis was uncontrolled pulmonary involvement longer than 4 months. Since the brain metastases are characterized by haematogenous spread, one would expect also pulmonary involvement for most cases, who have cerebral metastases. However, in our series only two cases had concurrent brain and pulmonary metastases diagnosed by contrast enhanced CT scans. Since, multiple organ involvement, including the bone marrow was seen in all our cases, possible explanation of this phenomenon could be that either the lung involvement was undetectable employing current diagnostic methods or the lungs were not fertile organs for metastatic deposits of these tumours.

Among the 154 patients, 18 cases had lung metastases, and 16 of them harboured the lung lesions more than 4 months. Only 2 of these 18 cases had brain metastases. Moreover, in spite of 36.3% pulmonary involvement, we saw only one case with brain metastasis of sarcoma (angiosarcoma) among the 40 sarcoma cases (OS, ES and soft tissue sarcomas). Our data also support the soil-seed hypothesis for brain metastasis.

Surgical removal should be the treatment of choice for patients with solitary lesions. Although surgical management of multiple and recurrent brain metastases has been recommended in adults [3], the same protocol has not been established for children yet. It is reasonable, however, to consider excising a metastatic lesion that is immediately life-threatening or incapacitating, even though additional metastatic brain lesions may be present.

There have been occasional reports of children surviving cerebral metastases [16, 17]. We recommend aggressive treatment (surgery, chemotherapy and radiotherapy) for paediatric intracranial parenchymal metastases from solid tumours, especially if the primary tumour and other metastases have apparently been under control. Prophylactic CNS radiotherapy for solid tumours is not recommended [6]. Unfortunately, in our series, none of these 7 cases lived more than 1 year, and 6 of them died due to progression or relapse of the cranial disease.

In conclusion, the incidence of paediatric intracranial parenchymal metastasis is 4.5% in this series.

Prognosis is poor and intracranial disease is the primary cause of death.

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Comment

Considering the rarety of metastatic lesions in the pediatric population, this paper – which presents 12 cases of metastasis – is very interesting. The study is original and well conducted; the discussion is excellent.

The epidemiologic interest of such a series is obvious.

M. Choux

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